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THE APPLICATION OF ELECTRICAL CURRENT IN DENTAL ANESTHESIA.(U)
APR 77 B S SAVARA, R W FIELDS, R B TACKE DADA17-70-C-0075

UNCLASSIFIED NL

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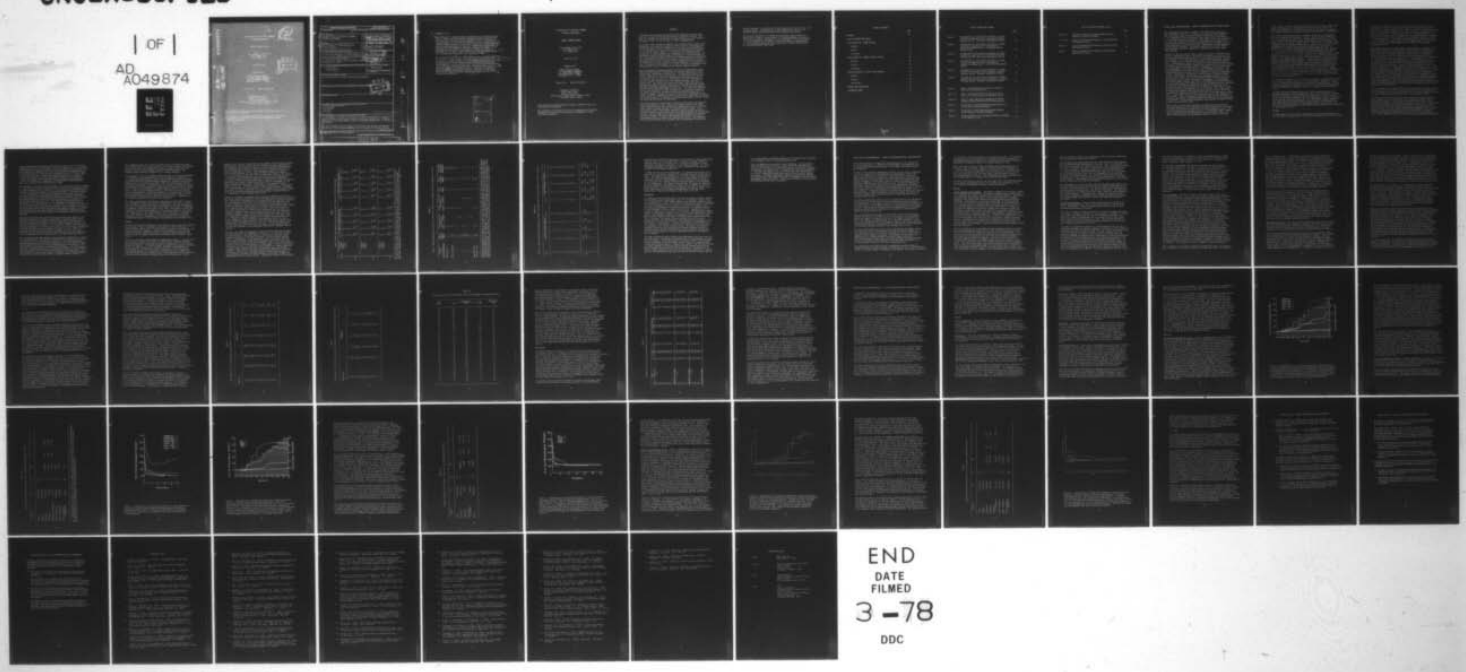
AD A049874



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APPLICATION OF ELECTRICAL CURRENT IN DENTAL ANESTHESIA

ANNUAL SUMMARY REPORT

B.S. SAVARA, D.M.D., M.S.
K.W. FIELDS, Ph.D.
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April 25, 1977

Supported By

DENTAL RESEARCH BRANCH
U. S. ARMY MEDICAL RESEARCH
AND DEVELOPMENT COMMAND
Washington, D.C. 20315

Contract No. DADA-17-70-C-0075

Biophysics Laboratory
Child Study Clinic
School of Dentistry
University of Oregon Health Sciences Center
Portland, Oregon 97201

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER

2. GOVT ACCESSION NO.

3. RECIPIENT'S CATALOG NUMBER

4. TITLE (and Subtitle)
THE APPLICATION OF ELECTRICAL CURRENT IN DENTAL ANESTHESIA.

5. TYPE OF REPORT & PERIOD COVERED
1 April 1976 to 31 March 1977 Annual Summary Report.

6. PERFORMING ORG. REPORT NUMBER
1 Apr 76-31 Mar 77

7. AUTHOR(s)
Bhim S. Savara, R. Wayne Fields, and Richard B. Tacke

8. CONTRACT OR GRANT NUMBER(s)
DADA-17-70-C-0075

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Biophysics Laboratory, Child Study Clinic, School of Dentistry, University of Oregon Health Sciences Center, 611 S.W. Campus Drive, Portland, OR 97201

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
62110A
3A162110A825 00 014

11. CONTROLLING OFFICE NAME AND ADDRESS
US Army Medical Research and Development Command
Washington, DC 20314

12. REPORT DATE
25 April 1977

13. NUMBER OF PAGES
61 pages

14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)
61p.

15. SECURITY CLASS. (of this report)
UNCLASSIFIED

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)
Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)
Orofacial Electroanalgesia
Local Analgesia
Pain Control
Tooth Pulp

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
Our present work concerns the electrical control of orofacial pain (Electroanalgesia (EA)) by two entirely distinct physioligcal mechanisms. To date, the tooth pulp has been used as a model of general orofacial pain in all of our studies.

One mechanism, Gating Block EA, involves diffuse, low intensity stimulation of orofacial skin or mucous membranes, and is apparently effective through

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DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

20. ABSTRACT (cont.)

the interaction of multiple sensory modalities in the central nervous system. Human experiments using experimental pain have demonstrated that this form of EA has definite analgesic effects, characterized certain features of electrical waveforms and sites of stimulation, and permitted the attainment of institutional sanction to cautiously begin tests on pathological pain in patients. Concurrently, experiments in behaving cats have just been initiated, following development of the experimental model, and are being used to continue the study of waveforms and anatomical sites. Effective EA has been demonstrated using subcutaneous stimulation near the mental foramen.

The second mechanism, Receptor Block EA, involves localized stimulation at the focus of pain origin. Such effects have historically been attributed to anodal blockade, but our remarkable success with a novel pulsating direct current waveform suggests more subtle mechanisms having superior clinical practicality. The experiments have involved acute recording procedures from single pulp-driven units of the Gasserian ganglion in anesthetized cats. Using our novel pulsating waveform, we have demonstrated analgesia equivalent to continuous direct current while virtually eliminating the serious side effects of the latter waveform.

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ABSTRACT

Peripheral nerve transmission and perceptual awareness associated with pain can be controlled by the application of electrical current. Our goal is to assess the feasibility of using electrical currents (Electro-analgesia, or EA) to control acute or chronic orofacial pain.

Our present work concerns two specific and entirely distinct pain control mechanisms. One mechanism, Gating Block EA, involves a distributed low current-density electrical stimulation of the skin or mucous membranes, and is believed to be effective by virtue of intermodality interactions in the central nervous system, to interference with peripheral nerve conduction, or, more probably, to a combination of both mechanisms. The second pain control mechanism under investigation is Receptor Block EA. The latter technique features localized, low-power electrical stimulation, and is believed to be effective by virtue of interference with receptor mechanisms at the level of actual sensory transduction and/or the block of conduction in initial portions of primary afferents. To reiterate, our work is directed to the study of two totally distinct EA mechanisms, and, realistically, should be viewed as two entirely separate projects.

The Gating Block EA program presently involves two experimental series, Human Psychophysiological Experiments and Chronic (Behavioral) Psycho-physiological Experiments, respectively. The Human Experiments of the present contract year were directed first to the study of the efficacy of EA in relation to electrode configurations and anatomical sites of stimulation, and, secondly, to a comparison of the best configuration and site thereby identified with our standard intraoral site used historically. The latter tests were particularly important since the optimal site identified had an extraoral location and therefore offered important advantages regarding accessibility. The Chronic experimental model has been under development for some time. Its principle importance follows from the ability to test analgesia at the perceptual level and the greater flexibility afforded by animal models permitting tests not allowed in humans. During the present contract year, development of the Chronic model was completed and data was collected to quantitatively define its characteristics. In addition, preliminary data derived from the initial definitive EA experiments are described.

The Receptor Block EA program has exclusively involved Acute Neurophysio-logical Experiments to date. Work of the present contract year first established the feasibility and potential advantages of using a pulsating direct current waveform instead of continuous direct current. This represented a major breakthrough, because we have previously shown that continuous direct current, while effective, induces significant irreversible effects. The pulsating direct current waveforms permitted circumvention of these problems. The latter experiments were followed first with an experimental series to identify the optimal duty cycle of the pulsating direct current waveform, and, secondly, with an experimental series just

recently completed to identify the optimal frequency of the pulsating direct current waveform. Investigations of alternating current EA are to be initiated shortly and may provide further waveform improvements.

The military significance of Gating Block EA and/or Receptor Block EA is significant in terms of potentialities of increased manpower efficiency, reduction of analgesic contingencies, and enhancement of the effectiveness of various therapeutic procedures. These objectives are being obtained in a cost-effective manner by cross utilization of skills and facilities in a multidisciplinary team effort.

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GATING BLOCK ELECTROANALGESIA: HUMAN PSYCHOPHYSIOLOGICAL INVESTIGATIONS

The Gating Block EA program is based on the "Gate Control Theory" of pain, proposed in 1965 (1). In essence, Gate Control Theory suggested that the various somatic modality channels, historically considered to be independent, actually exhibited significant interactions as early as the initial synaptic relay centers in the spinal cord. The interactions were such that concurrent activity in other modalities attenuated the transmission of afferent activity associated with pain, whereas, in contrast, continued nociceptive inputs were considered to be self-enhancing through positive feedback. The original paper on Gate Control Theory also proposed a functional schematic of the spinal cord interactions involving pain.

Proposal of the Gate Control Theory triggered a flurry of interest and a wealth of experimental work. The theory was extremely attractive in that it functionally explained many aspects of pain which previously had been quite obscure (2,3). Some workers took the proposed functional schematic too literally and rejected the theory based on isolated inconsistencies (4,5). Nevertheless, a wealth of information from single-unit studies in the spinal cord and Trigeminal complex has confirmed the functional concepts of the Gate Control Theory and led to a monumental increase in the level of understanding of the organization of pain pathways (2,4,6-16). Pain can be attenuated by activity in other afferent modality channels, and combinations of such activity can be optimized for analgesic effectiveness (11-13). Furthermore, information on interactions occurring in higher centers of the central nervous system is accumulating rapidly (2,3,17). In particular, at the level of the thalamus, three nuclear centers have been shown to participate in nociceptive mechanisms. Certain elements of the ventro-basal complex (VB) seem to be predominantly associated with the Sensory-Discriminative dimensions of pain, whereas particular components of the CM-Pf-intralaminar complex (MT for Medial Thalamus) and of the Posterior Nuclear Group (PO) have been predominantly associated with the Motivational-Aversive dimensions of pain (2,4,9,10). Also, there seems to be significant feedback interactions between MT and PO (16), and PO has been shown to communicate principally with SII of the somatosensory cortex (17), a center which has also been associated with aversive responsiveness to pain (18). Thus a strong and evergrowing foundation of information supporting and further elucidating Gating-type interactions is accumulating as the result of acute animal experiments investigating nociceptive neural activity at the cellular level.

Many studies of Gating Block analgesia in humans have shown that the perceptual experience associated with experimental pain can be attenuated or blocked by electrical stimulation of the same dermatome (19-21). The electrical stimulation employed has been of a distributed nature commonly near a peripheral nerve (Transcutaneous Nerve Stimulation, TNS). Most reports have explained the experimental results in terms of the Gate

Control Theory or similar central interactions, but one study claims significant contributions by a peripheral nerve blockade (21). Thus, the perceptual consequences of Gating Block EA may be the result of a mixture of peripheral and central effects, depending upon individual circumstances.

Data related to pathological pain in humans, as opposed to experimental pain, is voluminous by comparison. Primary interest in such studies was initially concerned with the use of dorsal column stimulation to relieve chronic pain, a technique involving the implantation of a stimulator with leads placed on the dorsal columns (22-25). The rationale of dorsal column stimulation was an attempted attenuation of pain by virtue of Gate Control mechanisms in the spinal cord, accessed via antidromic activation of ascending collaterals of non-nociceptive primary afferents (25). As use of dorsal column stimulation matured, cutaneous stimulation was employed to orthodromically activate the same non-nociceptive inputs to Gating mechanisms in an attempt to evaluate candidates for potential dorsal column implants, and the general efficacy of TNS was subsequently realized (25). Dorsal column implants have provided varying degrees of success, and their present use is predominantly limited to a small fraction of patients exhibiting certain chronic pain syndromes. TNS also has exhibited differing degrees of success to date (25-33), apparently because of variations in the efficacy of particular waveforms and stimulus configurations relative to appropriate activation of the requisite neural structures (the exact fibers subserving optimal interactions are still unidentified). Besides our studies using experimental pain and our preliminary tests of pathological pain in humans (34), only one preliminary report remotely related to the electrical relief of orofacial pain in humans using Gating Block stimulus formats has been reported (19).

The literature relevant to Gating Block EA indicates a significant potential for effective clinical utility, a conclusion strongly supported by data from our laboratory previously reported (34) and presented below. Further studies are required to delineate the specific efficacy of particular waveforms and application strategies relative to defined clinical pain conditions.

The Human Psychophysiological Experiments of the present contract year employed experimental pain induced by the electrical stimulation of intact teeth, the application of EA through electrodes applied to the surfaces of the skin or mucous membranes, the use of perceptual indices of sensibility based on verbal reports, and the use of an experimental design compatible with Signal Detection Theory formats of data analysis and interpretation. This work completes the study of experimental pain; future work is to be directed to the investigation of pathological pain in human subjects presenting to institutional clinics.

Methods

The human model for the study of experimental pain involved adaptations of clinical pulp vitalometry (35), the electrical stimulation of teeth to assess

the status of pulpal health. The voltage required for threshold sensory perception in a tooth is clinically related to the health status of the pulp (36). In normal, healthy teeth, found in our specially selected human subjects, the voltage threshold for sensory perception is indicative of the level of excitability in pulpal nerve fibers. In an uncompromised tooth responsive to normal levels of stimulation, the administration of analgesic agents (or EA) will raise the threshold of stimulation required to induce perceptual experience. Our general experimental model involved the electrical stimulation of normal intact teeth in human subjects, using verbal reports of their perceptual experience as an index of the analgesic effectiveness of EA.

Experimental protocols and data analysis were designed in accordance with Signal Detection Theory, a theoretical construct recently introduced to Psychophysics permitting the quantitative separation of changes in attitudinal bias from true changes in sensory acuity (37,38). Five sensory categories and four stimulus intensity levels were employed. The five sensory categories were: 1), no sensation; 2), possibly a faint sensation; 3), a definite but innocuous sensation; 4), intermediate pain; and 5), moderate pain. For each experimental trial, the subject was asked to categorize his sensory experience following the presentation of one of the four stimulus intensities. The four stimulus intensities were determined for each subject at the beginning of each experiment to be: 1), zero stimulus intensity; 3), threshold of sensation; 5), moderate pain; and 4), a stimulus intensity intermediate between levels (3) and (5). An extra sensory category designated 2) was provided slightly below threshold to add flexibility of interpretation, but there was no corresponding level 2) of stimulus intensity. The subject was notified of an impending stimulus by a signal light, permitting the inclusion of the zero intensity stimulus level. The Signal Detection Theory design involved the use of sensory categories spanning the range of sensation in the requisite modality (37,38), rather than merely relying on the traditional techniques limited to determinations of threshold (39).

The key elements of the human experimental pain model were the use of tooth pulp as the source of orofacial pain (a pure pain source uncontaminated by other modalities), the use of a perceptual (not a reflex!) index of pain, and the use of Signal Detection Theory formats of experimental design.

Stimulation of the tooth pulp to elicit potential perceptual responses (test stimulation) was accomplished using a specially designed acrylic appliance custom-made to fit the anterior maxillary dentition of each experimental subject, as described in a previous report (36). The appliance was required to eliminate moisture accumulation which could alter the effective electrode area, and to permit rigorous reproducibility of electrode position. One test stimulus electrode was embedded in the acrylic appliance, and was moistened with an electrolyte medium to insure an efficient and uniformly distributed contact area (40) of approximately 4 mm. Test stimuli were applied to the tooth in the monopolar configuration

through the appliance electrode, referenced to a large (2 cm X 2 cm) plate placed remotely on the dorsal aspect of the ipsilateral neck. All electrode materials were platinum, to minimize effects of electrode polarization (41). Test stimuli were composed of a train of bidirectional rectangular pulses of 40 percent duty cycle and 200 pps frequency, with a total train duration of 60 ms per stimulus. Bidirectional pulses were employed to reduce the effects of iontophoresis. Test stimuli were derived from a specially designed photically-isolated battery-powered constant-current generator, driven by one channel of a Neurodyne 1550 Bidirectional pulse generator which also had photically-isolated output stages.

EA stimulation (34) involved the placement of a 4 mm X 10 mm active electrode at a particular intraoral or cutaneous facial site (protocols detailed below) to induce analgesia, and a large (2 cm X 2 cm) indifferent electrode placed remotely on the dorsal aspect of the ipsilateral neck. For reasons similar to those associated with the test electrodes, electrode paste was used at all contact interfaces, platinum was employed as the electrode material, and bidirectional pulse waveforms were universally employed. The 'standard' EA waveform involved a train of bidirectional pulses at a frequency of 100 pps and 50 percent duty cycle. The intensity was determined at the beginning of each experiment to be just subthreshold (important because placebo effects could be ruled out). Periodically, EA intensity was checked to verify that it was still just subthreshold. Once initiated, EA stimulation was applied continuously during the experimental session. EA stimuli were derived from a photically-isolated battery-powered constant-current generator driven by the second channel of the Neurodyne Bidirectional pulse generator.

Experimental subjects were recruited from the student body campus of the Health Sciences Center by general advertising. Potential subjects were examined to insure the presence of anterior maxillary dentition free of defects as determined by visual inspection and radiographic analysis, and were interviewed for suitability. Once accepted, a subject was presented a written description of the project and his or her role therein, accompanied by verbal elaboration, and the subject was asked to sign a consent form (prepared in conjunction with an Army attorney). Also, at that time, impressions of the anterior dentition were obtained, permitting manufacture of the custom-made acrylic dental appliance for that particular subject.

Once the appliance became available, the subject was scheduled for a series of training sessions. The initial training session involved general familiarization with test tooth and EA stimulation. The remaining training sessions involved a preliminary determination of the four stimulus levels (tooth stimulus levels 1, 3, 4 and 5) appropriate for the subject on that particular day, followed by the definitive experiments. The latter were composed of repeated episodes of 14 stimulus presentations, one presentation every 20 seconds, with a balanced randomization of stimulus levels. For each stimulus, the subject was asked to categorize the perceptual response relative to the five available sensory categories (sensory levels 1-5).

The training sessions were completely devoid of any EA stimulation, and were continued until the subject achieved a sufficient degree of performance reliability, reporting the appropriate sensory category relative to the presented level of tooth stimulus intensity in 90-95 percent of the stimulus trials (generally achieved in 3-5 training sessions).

To determine the four test stimulus intensities used for a given experiment, the threshold to pulp stimulation was first recorded as the average of six independent determinations, three using an ascending series of stimulus intensities and three using descending intensities. Threshold represented stimulus level 3), and was not painful. Next, successively more intense stimuli were presented to determine level 5), the point at which the subject felt moderate pain and past which he would have felt extreme and intolerable pain. Level 4) was identified as halfway between levels 3) and 5), and level 1) was the zero stimulus intensity. Once the four tooth stimulus levels were determined, two baseline episodes of 14 stimuli were conducted using randomized test stimulus intensities in the absence of EA, to verify the subjects reliability and to establish control levels. Subsequently, the particular definitive EA protocol was conducted.

Two distinct experimental series were conducted during the 1976-77 contract year, designated Phase I and Phase II, respectively. The Phase I studies were directed to a preliminary survey of particular electrode configurations and sites of stimulation, the latter sites chosen on the basis of seemingly low-impedence access to deep tissues of the face. The Phase II studies were composed of a quantitative comparison of the optimal extraoral site versus the optimal intraoral site identified as the most effective in the Phase I work. The purpose of the Phase II effort was to test whether extraoral stimulation could be substituted for intraoral application, an important consideration because of the increased accessibility of the extraoral site.

Results

The Human Gating Block experiments of the present contract year were composed of two phases. Phase I experiments systematically surveyed the use of electrode arrays and the use of various anatomical sites of stimulation. The Phase II effort was composed of a quantitative comparison of the two best stimulus locations identified in Phase I, being the Oral Mucosa near the test tooth and the dermis overlying the ipsilateral Mental Foramen, respectively.

The Phase I electrode array studies are summarized in Table I. The electrode array studies focused on two sites of EA application, the Mental Foramen and Oral Mucosa (A and B sections of Table I, respectively), the sites also employed in Phase II. The Mental Foramen experiments were actually conducted late in the contract year after trends of the Phase II experiments had become apparent. An electrode "array" consisted of a 6 mm^2 electrode in the standard position for the particular stimulation site, an identical electrode placed distally (medially) with a 6 mm separation, and an identical electrode placed proximally (laterally) with a 6 mm separation. EA was

applied to the central electrode alone, the central and the distal electrode simultaneously, and the central and the proximal electrode simultaneously. Our equipment was incapable of driving all three electrodes simultaneously. The results of Table I indicate that the use of electrode arrays did not result in improved EA efficacy. The experimental numbers are small for each condition studied, as the results obviously indicated no dramatic effect of electrode arrays, and further studies were deemed of low priority and unworthy of further pursuit. The data did reveal one important fact. The distal-standard electrode combination produced results comparable to the use of the standard electrode alone. Based on the latter information, additional tests using a single electrode but shifted 6 mm medial to the Mental Foramen indicated results comparable to the standard electrode position ($p > .10$). Therefore, with the Mental Foramen site, there appears to be some flexibility in the position of the single electrode. Regarding the concept of arrays in general, the lack of improved effectiveness coupled with the technical problems associated with multiple electrodes has led to a cessation of their consideration and use.

Results of the Phase I anatomical sites survey are summarized in Table II. The latter studies involved four active electrode sites in various ipsilateral and contralateral combinations of active and indifferent electrode positions. Four orofacial sites were selected as candidates for EA evaluation based on their proximity to the site of initiation of the experimental pain, to anatomical structures deemed likely to provide current access to deep tissues, or to locations near major sensory nerve trunks. The sites chosen for study were respectively, the buccal Oral Mucosa near the test tooth, an Intraoral Salivary Foramen, and cutaneous locations over the Infraorbital and Mental Foramina. The two most effective sites were found to be the ipsilateral Mental Foramen and the Oral Mucosa near the test tooth (Table II). During EA, reported intensities were reduced in 66% and 56% of the trials compared to values expected in the absence of EA for the Oral Mucosa and Mental Foramen stimulus locations, respectively, results which demonstrated a significant EA effect ($p < .01$). The effectiveness found in these tests was less than that of the Phase II effort because fewer sessions were included in each experiment (the overall induction time was shorter).

Results of the Phase II comparison of the Oral Mucosa and Mental Foramen EA stimulation sites are summarized in Table III. In Table III the data has been analyzed to show the percent of trials which indicated an EA-dependent alteration of perceived intensity, relative to that expected based on the magnitude of test stimulation. As in all human protocols, each EA session during an individual experiment consisted of 12 EA test trials (and two control trials in the absence of EA). The values shown in the table for each session indicate the total number of the 12 trials which exhibited an EA effect, an EA effect being defined as a subject reporting a higher sensory category than that expected based upon test stimulus intensity. Inspection of the figure reveals that EA applied to both the Oral Mucosa and the Mental Foramen resulted in significant EA effects, although during induction, the effectiveness of the Mental Foramen site lagged behind that of the Oral Mucosa. Statistical analysis of the results

TABLE I

Phase I Human Experiments Testing the Relative Efficacy of Electrode Arrays

Nr	Electrode Array	A: Mental Foramen Sessions 1	2	3	4	5	B: Oral Mucosal Sessions 1	2	3	4	5
1	Central	0	0	3	4	7	2	4	7	9	10
2	only	1	0	4	5	5	0	1	5	7	8
3		1	2	5	6	8	2	5	8	10	10
4		0	0	4	5	7	--	--	--	--	--
5		1	3	4	7	8	--	--	--	--	--
$\bar{x}$		0.6	1.0	4.0	5.4	7.0	1.3	3.3	6.7	8.7	9.3
S.D.		0.6	1.4	0.7	1.1	1.2	1.2	2.0	1.5	1.5	1.2
%		5	8	33	45	58	11	28	56	72	78
1	Central	0	3	4	7	8	1	3	6	9	10
2	plus	1	1	6	5	8	2	1	4	3	5
3	Distal	1	0	4	5	7	0	3	3	5	6
4		0	4	3	6	8	--	--	--	--	--
5		1	3	5	8	7	--	--	--	--	--
$\bar{x}$		0.6	2.2	4.4	6.2	7.6	1.0	2.3	4.3	5.7	7.0
S.D.		0.6	1.6	1.1	1.3	0.6	1.0	1.2	1.5	3.1	2.7
%		5	18	37	52	63	8	19	36	47	58
1	Central	1	0	3	4	6	1	3	3	5	6
2	plus	0	0	2	3	4	0	1	3	3	5
3	Proximal	0	2	5	7	7	0	0	5	5	8
4		1	3	3	4	5	--	--	--	--	--
$\bar{x}$		0.5	1.3	3.3	4.5	5.5	0.3	1.3	3.7	4.3	6.3
S.D.		0.6	1.5	1.3	1.7	1.3	0.6	1.5	1.2	1.2	1.5
%		4	10	27	38	46	3	11	31	36	53

For all conditions, there was a significant increase in EA efficacy during the series of sessions ($p < .01$), and the single central electrode was equivalent or superior ($p < .01$) to the paired electrode configurations for the Mental Foramen and the Oral Mucosa stimulation sites, respectively.

TABLE II

Phase I Human Experiments Testing the Relative Efficacy of Various Orofacial Anatomical Sites

Location of Active Electrode	Exptl. Protocol Number	Active Electrode laterality ipsi-	Active Electrode laterality contra-	Indiff. Electrode laterality ipsi-	Indiff. Electrode laterality contra-	Total Nr Subjs.	Total Accepted Expts.	% decrease perceived intensity
Oral Mucosa	I	X		X		3	11	68
"	II	X		X		3	9	63
Mental Foramen	III	X		X		3	14	56
"	IV	X		X		3	5	56
"	V		X	X		5	5	--
"	VI		X	X		2	2	--
"	VII	X			X	4	4	--
"	VIII	X			X	3	3	--
"	IX		X		X	2	2	--
"	X		X		X	2	2	--
Salivary Duct	XI	X		X		5	13	--
Infraorb. For.	XII	X		X		4	12	--

Protocols I-II and III-IV appear to be identical from the Table because they involved the same experimental conditions summarized in the present form. They were actually distinct protocols in that different aspects of electrode array tests were involved. Protocols XIII-XVI (unlisted) also involved investigation of the electrode array problem. Protocols where the "% decrease in perceived intensity" results are omitted means that the actual data deviated by 7% or less from basal values and the data was not analyzed further.

TABLE III

Phase II Human Experiments Comparing the Mental Foramen and Oral Mucosa Sites of EA Application

Nr	Mental Foramen Session				Gingival Mucosal Session				
	1	2	3	4	1	2	3	4	5
1	1	6	8	9	5	8	8	9	12
2	2	5	6	9	8	11	11	10	11
3	1	5	8	10	7	7	9	10	12
4	0	3	5	9	6	9	11	11	12
5	1	4	8	10	8	8	10	10	12
6	1	3	7	9	9	10	9	10	11
7	0	4	5	10	4	7	10	10	11
8	0	4	6	11	10	11	12	12	12
9	1	4	5	9	6	10	10	10	11
10	1	5	9	11	--	--	--	--	--
x	0.8	4.3	6.7	9.7	7.0	9.0	10.0	10.2	11.6
S.D.	0.63	0.85	1.49	0.82	1.94	1.58	1.23	0.84	0.59
%	7	36	56	81	58	75	83	85	96
t	--	--	--	--	9.84	8.10	5.40	1.44	--
p	--	--	--	--	$<.001$	$<.001$	$<.001$	$>.10$	--

indicated that the Mental Foramen site did not differ in effectiveness when compared to the Oral Mucosa EA stimulus location following comparable induction times ($p > .10$, Table III), a significant finding in view of the greatly increased accessibility of the former placement. The latter comparison was based on the session 4 data, as session 5 data was not available for the Mental Foramen site.

The Phase II data can also be subjected to a second analysis based on the magnitude of the sensory category shift observed during each effective EA trial. This analysis was discussed in our recent Contract Renewal Application, the results being quantified as the average number of sensory categories involved in EA-dependent shifts of reported perceived intensities relative to the sensory categories expected based on the magnitude of test stimulation. The results indicated that following full induction, the Mental Foramen site resulted in superior EA as compared to the Oral Mucosa location. An observed average change of 2.0 and 1.5 sensory categories was observed for the Mental Foramen and Oral Mucosal sites, respectively, values which differed statistically ($p < .01$).

Discussion

In conjunction with previous reports (34,36), our results indicate substantial EA effects using subthreshold levels of EA intensity, thereby ruling out placebo effects. This finding represents an extremely powerful result not originally anticipated. All reports of significant effects of peripheral electrical stimulation for the control of pain in the literature have indicated the requirement for suprathreshold levels of stimulus intensity for even marginal levels of effectiveness (23-33). Explanations of the results of regional or local effects of electrical stimulation have usually invoked the Gate Control theory of pain (4,25) or some modification thereof. However, one prominent laboratory has demonstrated the existence of peripheral blocks resulting from typical peripheral pain control stimulation (21). Therefore, the results reported presently may result from a peripheral block, or, alternatively, some combination of peripheral block coupled with a conduction or a central Gating type blocking mechanism. In this regard, it is important to realize that afferent activity may still be impinging on the central nervous system in the absence of perceptual awareness, since the particular EA-induced spatio-temporal pattern of afferent activity may be insufficient to activate perceptual mechanisms but nevertheless adequate to induce significant effects in the central nervous system.

The Human Psychophysiological model using experimental pain has served our objectives well. In addition to demonstrations of effectiveness, the model has also permitted the identification of certain parameters of EA administration including, during the present contract year, the ineffectiveness of multiple electrode arrays, a quantitative survey of the relative efficacy of several anatomical stimulation sites, and the demonstration that the Mental Foramen(extraoral) site of EA application can be substituted for the Oral Mucosa (intraoral) site which we have used historically. Finally, based on the experimental pain data, we have now obtained official sanction

of the Human Rights and Welfare Committee of the institution to proceed with preliminary tests involving pathological pain.

Thus, the Human work has reached a major milestone. We have finally acquired institutional sanction to begin definitive experiments to characterize the efficacy of Gating Block EA on specific pain problems presenting to the dental clinic. Simultaneously, additional anatomical and waveform investigations can be conducted much more efficiently in the Chronic Psychophysiological model which has just recently become operational. The Human experiments combined with additional waveform and administration improvements afforded by information from the Chronic experimental model will permit a quantitative definition of Gating Block EA feasibility within one to two years.

GATING BLOCK ELECTROANALGESIA: CHRONIC PSYCHOPHYSIOLOGICAL INVESTIGATIONS

The overall concept of Gating Block EA was discussed in the introduction of the previous section on Human Psychophysiological Investigations, but the latter discussion applies equally to the Chronic Psychophysiological Investigations.

Perhaps the most powerful experiments available for the study of analgesia are Chronic (Behavioral) Psychophysiological Experiments, because they permit the evaluation of central nervous system functions free from complications introduced by anesthetic agents and surgical interventions associated with Acute experiments, and they permit more flexibility than studies in humans. They are also crucial to verify information derived from Acute experiments at the perceptual level, to identify pathways and mechanisms, and to obtain data crucial for the documentation of safety. The central feature of the Chronic experimental model is the use of perceptual rather than reflex manifestations of sensation as an index of EA effectiveness. To adequately study the efficacy and feasibility of orofacial Gating Block EA, a model is required in which the animal can report pain tolerances (based on perceptual criteria) on a continuous basis over an extended period of time.

The Chronic experimental model has as its central features the implantation of electrodes in a tooth pulp to permit application of noxious stimuli, the implantation of electrodes at specific sites selected for EA application to permit study of the analgesic efficacy of such stimulation, the implantation of a head pedestal allowing electrical communication with external apparatus, and the use of a perceptual as opposed to a reflex index of pulpal perceptual sensibility.

Noxious stimulation is initiated by activation of tooth pulp afferents because the tooth pulp provides a source of pure pain, it is an adequate generalized model of orofacial pain, and it is readily accessible (42). Tooth test stimuli are administered to the same tooth (maxillary canine) and in the same manner (0.1 ms rectangular pulses in the bipolar stimulus configuration and a train-stimulus mode) as that used for acute experiments involving pain pathways reported in the literature (6,7,12-15).

The site of EA stimulation for the initial definitive experimental series was selected to be at a subcutaneous site near the Mental Foramen, the site identified as the optimal extraoral stimulus location from locations examined in prior Human experiments. Furthermore, the EA stimuli were administered in a similar fashion (electrical stimuli applied in a distributed stimulus geometry near the Mental Foramen) and using a similar electrical waveform to that employed in the prior human experiments, to provide maximum overlap with the latter experimental data.

All experiments were conducted using standardized psychophysiological stimulation and recording techniques, and employed the cat as the experimental animal for economy, maximal correlation to the general pain control literature

(6,7,17,43-53), and previous work in our laboratory (54-60). The particular experimental model chosen utilizes the Threshold Titration paradigm, an experimental procedure permitting the quantitative monitoring of perceptual sensibility in behaving animals over extended periods of time.

There have been no chronic animal experiments simulating Gating Block EA reported in the literature. However, important general information is available related to chronic models for the study of pain. Relevant techniques for the chronic stimulation of the tooth pulp as a source of pain have been described (45,49), as have models using perceptual indices of pain responsiveness (45,61,62). This information has been used extensively in the development of our Chronic Psychophysiological model.

The work of the present contract year involved, first, the final development of the Chronic experimental model, and, secondly, the initiation of the first definitive experimental series testing orofacial EA.

Methods

Animal Preparation and Surgery. Experimental animals were initially screened for suitability and subjected to preliminary training using a noxious foot-shock paradigm (see below), and were then scheduled for surgery. Endotracheal intubation was accomplished using a short-acting barbituate. Surgical anesthesia was induced under Ethrane-Oxygen and maintained using Ethrane-N_2O-Oxygen. Subsequently, an optically-coupled ECG (to preserve ground isolation) was attached (Terrasyn, Model N-IIIB ECG Isolation Amplifier), and a non-invasive blood pressure monitoring system was applied to one of the forelimbs (Hoffman-La Roche Arteriosonde, Model 1010). In addition, a Bechman LB-2 Medical Gas Analyzer, sampling the respiratory gases, was employed to continuously monitor end-tidal CO_2 as an index of short-term acid-base balance. Respiration was assisted on demand, or controlled, using a Bird Mark IV-VIII Anesthesia Assistor. Intraesophogeal temperature was monitored (YSI Model 43TA) and maintained at 38 $\pm$ 0.5 C by means of a heating pad with thermostatically controlled circulating water (Gaymar Temp-Pump System). The animals were then brought through the recovery process, and allowed several days to recuperate from the surgical procedure prior to the initiation of experiments. Long-term health status was documented through periodic physicals.

Noxious stimulation was accomplished through electrodes placed in the maxillary canine experimental tooth (45,55). One electrode was placed in each of two cavities drilled through the enamel to a near pulp exposure. The base of each cavity was dried, the electrode wire (stranded stainless steel) was spread out and packed in place, and the whole complex was sealed in position using non-conductive adhesive. One of the tooth stimulation electrodes was located on the lingual aspect and one on the buccal aspect of the tooth, both being near to but absolutely distinct from the gingival margin. The wire leads (teflon coated) were implanted under a muco-gingival flap, and then directed upward under the facial skin along the surface of the bone between the medial canthus of the eye and the nose, to gain access to an electrical connector mounted in the head pedestal (45). Initial training

sessions involved footshock as an alternative form of noxious stimulation, but no surgical procedures were required.

EA stimulation was accomplished using electrodes implanted subcutaneously near the Mental Foramen ipsilateral to the test tooth. The electrode wire was freed of insulation for several millimeters, and the uninsulated portion was looped to increase the area of exposed wire. This configuration was utilized to provide a distributed rather than focal stimulus geometry. The active EA lead was directed subcutaneously from the site of placement to the anterior surface of the head, for attachment to the electrical connector of the head pedestal. An indifferent EA electrode was placed subcutaneously in the ipsilateral neck, and was composed of a 1 cm length of bared wire, a large surface area being employed to greatly reduce current density relative to the active EA electrode.

The head pedestal to which the test tooth and EA leads projected was built up by repeated applications of dental acrylic, using methods adapted from a report in the literature (45). The acrylic pedestal was molded around stainless steel screws mounted in the skull of the animal. The lead wires were connected to a multipin electrical socket, which was then embedded in the acrylic pedestal. A flexible cable connected the pedestal plug to a multi-contact commutator suspended from a counter-balanced pulley system to provide minimal restrictions of vertical and rotational movements of the animal.

Stimulation Techniques. Three stimulus situations were involved in the Chronic experimental model, that of Footshock, Pulpshock, and EA stimulation, respectively. Special considerations related to each of these techniques are presently discussed.

Footshock of noxious intensities was used for initial training procedures (see below). Footshock consisted of the application of stimuli to aluminum bars in the lower portion of the cage at intensities determined to be definitely aversive independently for each animal prior to each experimental session (typically less than 0.2 ma). The stimulus waveform was a 60 ms burst of 4 equally-spaced rectangular pulses of 10 ms duration, with a burst repetition rate of 10 Hz.

An essential consideration relative to tooth stimulation was the use of a waveform providing for temporal summation of activity in pain pathways, a phenomenon recently realized to be important for nociceptive interpretation in the central nervous system (2,4,16). A train stimulus format was therefore adopted, to induce an activity profile in pulpal afferents which was somewhat despersed in time. Based upon our previous experimental determination of the Strength-Duration curve for pulpal afferents (55), 0.1 ms was chosen for the width of each rectangular stimulus pulse. The frequency of stimulation was selected such that a significant number of pulpal afferents could faithfully follow each stimulus pulse, based upon our data from single pulp-driven units in the Gasserian ganglion (59,60). The latter data indicated that the majority of the units responded faithfully to frequencies up to 300 Hz. Such high frequencies were also chosen

to accentuate perceptual as opposed to reflex responsiveness (63). Based upon these considerations, the waveform chosen for pulpal stimulation was a burst of four rectangular pulses of 0.1 ms duration at a frequency of 300 Hz, producing a burst duration of 10 ms.

EA stimulation requirements were entirely distinct from those related to tooth pulp stimulation. A variety of waveforms have been described in the literature (22,25,28). The latter information coupled with our previous human results indicate that waveform is obviously a very important variable for investigation, and the study of multiple waveforms is anticipated. The initial definitive experimental series involved the use of one particular waveform, a 100 pps train of bidirectional rectangular pulses at three different duty cycles, 3.16, 10.0 and 31.6 percent, respectively, identified as important in prior human studies. The proper intensity for EA stimulation was again obviously important based on our prior human experiments, but difficult to determine. For the initial definitive experiments, we chose to use an intensity somewhat below that which induced muscle fasciculations visible to the naked eye and, which, in the behaving animal, did not produce visible signs of perceptual discomfort.

Training Program. The desired Chronic Psychophysiological model had as its central feature the use of a perceptual index to monitor pulp threshold, the Threshold Titration paradigm of physiological psychology (61). The complicated nature of the latter procedure necessitated designing a training program in which the animals were directed through several preliminary behavioral training stages which successively approximated the desired paradigm. As an initial step, the animals were subjected to a Footshock paradigm in which noxious footshock (waveform previously described) could be terminated by pressing a lever. Animals deemed acceptable were then subjected to additional Footshock sessions until their performance reached a level of 80-90 percent escape behavior (typically 3-7 sessions). The animals were then taken to surgery, and the pulpal and EA electrodes, the lead wires projecting to the top of the head, and the head pedestal with its embedded electrical connector were implanted. Following recovery from surgery (2-3 days), the animals were subjected to at least one additional Footshock session to verify retention of previous training. The animals were then introduced to the next stage of training in which the site of noxious stimulation was shifted from the footpads to the tooth pulp, with all other parameters of the experimental paradigm unchanged. Pulp stimulus bursts (waveform previously described) were presented at a rate of 2.5 Hz and at an intensity determined to be definitely aversive prior to the training session. A transfer of training from Footshock to Pulpshock proved to be a relatively straightforward generalization process in many instances, but success in the Footshock training paradigm was not directly predictive of success in Pulpshock. Animals were deemed proficient in Pulpshock when performance at the 80-90 percent level of escape behavior was manifest. This usually occurred following 2-5 Pulpshock sessions.

Once training in the Pulpshock paradigm was deemed sufficient, the animals were introduced to the final procedure in the training series, the Threshold

Titration paradigm (61). A subthreshold intensity was used initially and repeated a given number of times (selectable), but following every N'th (usually 8) succeeding stimulus, the intensity was automatically incremented by a fixed (determinable) amount. Pulp stimulus bursts (waveform previously described) were presented at a rate of 1 Hz. In the absence of corrective behavior by the animal, this process continued with equal intensity increments after every N'th stimulus until noxious or potentially noxious intensities resulted in bar-pressing responses. A bar press was programmed to reset the stimulus intensity to zero. The experimental results have indicated that although there is a high degree of variability between successive responses, the animals show a strong tendency to maintain the same average tolerance level over prolonged time periods, results which are consistent with reports in the literature (61). Thus, the described procedure has provided a direct quantitative measure of perceptual responsiveness (threshold) to noxious stimulation over extended periods of time, an extremely powerful experimental capability. Finally, once the animals were deemed proficient in the Threshold Titration paradigm, EA stimulation protocols were introduced to test the resultant perceptual effects.

The various procedures associated with the Chronic Psychophysiological Experiments were accomplished in a specially designed experimental cage featuring provisions for footshock and access to the pulp and EA stimulating circuits while still permitting maximal animal mobility. The experimental cage was also designed to eliminate the animal's use of the walls to avoid footshock, to counteract the contingency of a continuous bar press which would render the procedure ineffective, and other practical problems. The entire experimental protocol, involving the presentation of stimuli and recording of responses, was controlled and recorded automatically during all Footshock, Pulpshock, and Threshold Titration paradigms. Automated behavioral training is termed "Automatic Shaping" (62), and, as described in detail below, is an experimental procedure which permits both a substantial acceleration of training and a significant reduction in personnel commitments. A microprocessor system has recently been introduced to control the Automatic Shaping procedures, replacing antiquated electronic control equipment employed previously.

Experimental Protocol. The Chronic Psychophysiological Experiments involved three successive stimulation paradigms, Footshock, Pulpshock, and Threshold Titration (the latter with or without accompanying EA). The animals were subjected to daily experimental sessions (excepting weekends) and were transferred to successive training stages as accrued proficiency permitted.

For Footshock sessions, the animal was placed in the experimental chamber and the Automatic Shaping microcomputer program was engaged. This resulted in the presentation of a train of stimulus bursts (waveform previously described) to foot bars in the lower section of the experimental chamber. The stimuli were continued for two minutes or until the animal pressed the response lever, at which time footshock was terminated. Footshock was derived from a constant-current generator (lab constructed) which supplied a given amount of current regardless of the number of foot bars that the animal happened to be straddling (64). A fixed rest interval of 30 sec was

provided between Footshock episodes, and the total duration of individual training sessions was 80 minutes. In general, during the first experimental session, the animals moved about aimlessly at first but very quickly developed an association between Footshock and the response bar as the result of accidental contacts with the latter object. Following more trials, they usually became fairly proficient in escaping footshock stimulation once it had been initiated, even in the initial experimental session. A signal light and an audio tone were presented simultaneously with Footshock to hasten training. Additional Footshock training sessions were continued until a level of 80-90 percent escape behavior had been attained. Animals were then identified as candidates for surgery, and the surgical procedure was scheduled. The results of our Footshock program (successful acquisition of escape behavior within 3-7 sessions in animals deemed suitable for the program) compared very favorably to results reported in the literature, which indicate that 5-10 sessions are required for successful escape training (65).

Following surgery, the animals were reacquainted to Footshock and then introduced to the Pulpshock paradigm. Pulp stimulus bursts (waveform previously described) were presented under the same Automatic Shaping format as that used for Footshock, but the intertrial rest interval was 50 sec rather than 30 sec. The animals were trained in repeated 80 min sessions, and the successful escape responses or failures to escape were recorded for the entire series of stimulus episodes. The criterion for success in the Pulpshock paradigm was performance at a level of 80-90 percent escape behavior, a situation usually realized after 2-5 experimental sessions in acceptable animals. A significant amount of attrition was manifest, however, because many animals successful in Footshock did not perform well in Pulpshock and were eventually rejected.

Animals successfully trained in Pulpshock were then introduced to the Threshold Titration paradigm, individual sessions of which lasted 80 minutes. Threshold Titration was the experimental procedure used for definitive EA experiments, but the latter were preceded by several sessions involving Threshold Titration in the absence of EA for initial orientation. As described previously, pulp stimulus bursts (identical to those used in the Pulpshock paradigm) were presented once per second with intensity increments introduced after every N'th (usually 8) stimulus. The approximate threshold for perceptual awareness of pulp stimulation was estimated at the beginning of each experiment, and the maximum intensity of the Threshold Titration output generator was set so that the threshold of that animal on that particular day was intensity step 3-5. At this point the microprocessor program was initiated, and the animal was maintained in Threshold Titration for the 80 minute experimental interval. The data was continuously recorded as stimulus intensity versus time on a chart recorder.

The initial definitive EA experiments completed to date have involved a series to characterize the optimal duty cycle of the bidirectional rectangular pulse waveforms. As with all other Chronic EA experiments to follow, the protocol involved a control period, a period of EA administration, and a post-EA recovery period, each of approximately equal duration. The

duty cycle experiments involved the administration of a continuous train of bidirectional rectangular pulses at a frequency of 100 pps. In any individual experiment, one of three duty cycles was investigated, being 3.16%, 10.0%, or 31.6%, respectively, values equally spaced logarithmically. This range of duty cycles was selected for examination based upon preliminary data from prior human experiments.

Results

Five categories of experimental results are presented, a description of the various facets of the Automatic Shaping selection and training procedures in their fully developed form, data documenting behavioral modification from Footshock to Pulpshock, data characterizing behavioral modification from Pulpshock to Threshold Titration, data characterizing the Threshold Titration paradigm itself, and, finally, the initial EA results.

In the Chronic Psychophysiological Automatic Shaping Experiments, the capability to study two types of behavior were programmed, escape behavior (the animal was permitted to terminate shock once it was initiated) and avoidance behavior (the animal was permitted to completely avoid shock). In an individual experimental session which was composed of a series of stimulus episodes, several time intervals were important: a), the intertrial interval (ITI), the interval between the termination of the aversive stimulus and the beginning of the next stimulus trial; b), the unconditioned stimulus interval (USI), the application of the stimulus of interest, in this case, the aversive stimulus; and c), the conditioned stimulus interval (CSI), in the present case, a signal light and/or audio tone which warned the animal of an impending stimulus. The CSI was used only when avoidance behavior was permitted. Avoidance behavior was permitted early in the overall program to evaluate the degree of learning during the development of training techniques, but was not used after routine training procedures had been established.

To summarize the training paradigms (identical for both Footshock and Pulpshock), in the case of avoidance training, a trial was initiated with CSI onset (the signal light and/or audio tone were presented in the absence of the noxious stimulus). If a response occurred within five seconds (avoidance behavior), the CSI was terminated and an ITI interval was initiated (45 seconds duration). If no response occurred within five seconds, the USI was initiated (while the CSI remained in effect). Both the USI and CSI were then terminated by a response (escape behavior), or alternatively, by time out of USI (one minute). In the case of escape training in the absence of the avoidance response possibility (a procedure used exclusively in the later periods of the program), CSI was bypassed, but otherwise the format was similar to the avoidance paradigm. If the animal was holding the bar down continuously at the initiation of CSI (or USI in the absence of avoidance behavior), and was still holding the bar down at USI time out, the response bar was energized for a few seconds to back the animal off the bar (bar-hot interval, BHI). A subsequent bar press by the animal or time out of BHI then led directly to another ITI interval. Experiments were automatically terminated at 80 minutes.

Threshold Titration training and EA sessions have not been placed under microcomputer control as of the present time. Rather, Threshold Titration control has been accomplished using a specially constructed Threshold Titration output generator triggered at regular intervals by a standard physiological stimulator. The output generator provides an isolated constant-current output and contains the logic circuitry controlling the automatic incrementation of stimulus intensity and the reset function required following an appropriate bar press response. The Threshold Titration output generator and its associated stimulator are to be replaced with a microcomputer system in the near future.

Data characterizing the Footshock training paradigm is presented in Table IV. The data dramatically demonstrate that the animals often achieved remarkable levels of escape behavior as early as the first experimental session. Animals moderately proficient in the first experimental session usually exhibited further increases in proficiency with additional experimental sessions, while animals demonstrating high levels of initial proficiency tended to maintain such performance levels. The data demonstrates the remarkably rapid training available using our particular adaptations of Automatic Shaping procedures.

Table V represents the raw data from Pulpshock training sessions. These experiments were conducted following the surgical procedures and reacquaintance of the animal with Footshock. Note that the Pulpshock results can be correlated directly with Footshock data from the same animal (Table IV). Fewer animals are represented in the raw data related to Pulpshock, as compared to Footshock, because of attrition related to microcomputer system development, surgical complications, animal failure to transfer to the successive paradigm, and other reasons. Accrued experience has permitted the reduction of such contingencies, but significant attrition will remain as an unavoidable aspect of the experimental model. The raw data of the table indicates that the animals rapidly developed a high level of proficiency in pulp-induced escape behavior in a manner analogous to the Footshock training results of Table IV. Some animals whose performance appeared to drop after several sessions, acquired a significantly higher level of proficiency in later experimental sessions, as exemplified by the data of animal # 65 of Table V. The raw data of the table and our experience to date demonstrate two facts. First, the generalization of behavior from the Footshock to Pulpshock is efficient and rapid, if successful at all. Secondly, acceptable animals respond with great proficiency in escape behavior following sufficient training in Pulpshock, verifying that the Pulpshock paradigm is operational.

The data of Table VI summarizes the results of experimental sessions in which the animals were trained in the Threshold Titration paradigm in the absence of EA. The table shows the raw data and normalized SEM (calculated as if the mean tolerance level was 100) for 27 experiments in five animals. The raw data indicates that there is a significant amount of variability in the averaged values of tolerated intensity levels over all Threshold Titration experiments. The variability is a fundamental characteristic of the experimental model. Nevertheless, the normalized SEM's indicate

TABLE IV

Percentage of Trials Exhibiting Escape Behavior in the Footshock Training Paradig...

Animal Nr.	Sessions 1	2	3	4	5	6	7
46	92	100	100	99	100	92	99
48	100	96	90	---	---	---	---
49	88	100	99	---	---	---	---
50	100	100	95	75	98	100	98
53	79	97	87	96	100	---	---
55	82	69	59	100	73	82	74
65	82	88	100	100	99	100	100
67	85	96	82	92	98	84	93
72	97	100	97	---	---	---	---
73	52	79	87	95	72	100	100
75	100	100	100	---	---	---	---
78	98	70	83	91	92	98	81

TABLE V

Percentage of Trials Exhibiting Escape Behavior in the Pulpshock Training Paradig

Animal Nr.	Sessions 1	2	3	4	5
46	---	---	---	---	---
48	68	64	---	---	---
49	97	98	98	98	76
50	85	100	100	---	---
53	95	---	---	---	---
55	54	36	63	46	53
65	84	85	70	76	71
67	78	82	93	80	100
72	87	76	77	62	88
73	87	83	58	---	---
75	44	94	93	97	73

TABLE VI

Characterization of the Threshold Titration Paradigm in the Absence of EA

Cat Number	Raw Data			Normalized SEM
	Nr	Avg	SEM	
50	91	12	1	8
50	39	23	8	33
50	30	15	5	41
50	61	32	4	14
65	41	36	9	25
65	39	28	7	25
65	16	109	84	77
66	83	46	10	22
67	52	155	34	22
67	74	19	4	21
67	77	37	8	21
67	27	82	39	48
67	30	41	10	24
67	16	134	52	39
67	24	64	20	31
67	19	86	24	27
67	29	70	19	35
67	30	140	34	24
67	15	170	76	45
67	28	46	14	29
67	18	107	24	22
67	24	51	13	25
67	32	43	11	26
67	61	39	5	13
75	103	34	12	35
75	52	15	2	13
75	23	37	5	14

that the variability can be reduced to acceptable levels if sufficient stimulus trials are included in the experiment, particularly in view of the marked effects exerted by EA (Table VII). In some instances, variability tended to change with time and occasionally became more pronounced near the end of an experiment, possibly reflecting periodic or eventual boredom or fatigue. This phenomenon is not believed to be the result of any EA effect resulting from test stimulation of the tooth pulp, based upon the results of our Acute Neurophysiological Experiments (56,58,59). The data of Table VI demonstrate the power of the present adaptation of the Threshold Titration paradigm for long-term monitoring of tolerance levels to noxious stimulation in behaving animals.

Table VII indicates the data analyzed to date from the initial definitive EA duty cycle experiments, in which duty cycles of 3.16%, 10.0% and 31.6% are being examined. The data includes 20 experiments in four animals, and was normalized for inter-experiment comparability by setting the average tolerance level of the control period equal to 100. The data is incomplete at this time, but several features are presently noteworthy. Combining all of the data from the three duty cycles, it is very clear that EA exerted a profound analgesic effect. In spite of the large variability, every EA and post-EA condition had an average effect exceeding a 100% increase in tolerance level with the exception of the 10% condition during EA, which exhibited a 49% increase. At this time, it appears that the 31.6% duty cycle exhibits the greatest effect, but this situation may change as additional data becomes available. Also, the 31.6% duty cycle waveform was equally effective in the EA and post-EA intervals. In contrast, the 10.0% and 3.16% EA waveforms showed a much smaller effect during EA than did the 31.6% duty cycle waveform, but the EA versus post-EA discrepancy of the former waveforms was markedly reduced during the post-EA interval.

Discussion

The conditioning and training of cats to escape or avoid noxious stimuli by pressing a lever is a valuable technique for the study of motivation and behavior (66) and to investigate various anesthetic or analgesic strategies (65). Typically, a procedure required for training animals to perform a specific response (operant) is referred to as shaping, and involves the prolonged and systematic reinforcement of behaviors (by an experimenter directly interacting with the animal) which at first may be dissimilar to the desired operant, but may be required to orient the subject animal toward the lever or toward a particular area in the experimental environment. Successive minor behavioral modifications are then introduced by the experimenter which more and more approximate the desired response. Finally, the actual operant itself is presented. This procedure is tedious and time consuming, since as many as 15 hours can be required with each animal for successive approximation training or "shaping" to, for example, escape aversive stimuli by pressing a lever (67).

An automatic and much abbreviated method for escape and avoidance conditioning, which circumvents the problems inherent in the basic shaping

TABLE VII

Definitive Duty-Cycle EA Experiments Using the Threshold Titration Paradigm

Cat	Duty Cycle (%)	Control			Electroanalgesia			Recovery		
		Nr	Avg	SEM	Nr	Avg	SEM	Nr	Avg	SEM
50	31.6	39	100	33	40	218	107	14	426	262
50		30	100	41	32	285	64	12	200	55
50		61	100	14	18	682	301	20	91	32
65		16	100	77	11	485	295	3	1555	1549
67		77	100	21	44	197	92	32	159	49
67		27	100	48	3	4135	1301	28	450	143
67		24	100	31	13	396	134	17	426	232
67		30	100	24	25	174	48	21	222	65
67		15	100	45	8	332	146	15	181	69
Weighted Averages		319	100		194	294		162	291	
67	10.0	30	100	24	36	129	37	41	146	45
67		19	100	27	17	244	86	14	280	124
67		28	100	29	15	202	49	12	434	130
67		24	100	25	24	149	35	19	169	37
67		32	100	26	18	153	33	17	451	79
75		52	100	13	49	113	13	43	253	47
Weighted Averages		185	100		159	149		146	253	
67	3.16	16	100	39	7	794	363	15	433	143
67		29	100	35	11	582	186	13	330	110
67		18	100	22	17	138	39	17	209	40
67		61	100	13	37	144	59	31	333	49
75		23	100	14	40	91	13	45	120	17
Weighted Averages		147	100		112	208		121	248	

procedure, is also available (62). Termed Automatic Shaping, this procedure eliminates the rigorous successive approximation format and significantly reduces the time necessary for conditioning. The experimental environment is rigorously structured such that the probability of eliciting the desired response from the animal is maximized. For example, if the interior dimensions of the response chamber and the location and site of the response lever are correctly determined, then within the first few stimulus trials, the animals exaggerated motor activity in response to, e.g., footshock will lead to contact with the lever and termination of the shock. Following a brief number of trials, the desired operant is often performed with regularity. Furthermore, and very importantly, this system can be automated.

The marked effectiveness of a rectangular pulse stimulus train of such a long duty cycle as the 31.6% waveform presently under investigation is difficult to explain. The latter waveform was chosen for examination because a similar effect had been noticed in preliminary studies using experimental pain in humans (34). In the first approximation, one would not expect the generation of much nervous activity using such a long pulse duration except at the leading and trailing edges of individual pulses. If the long duty cycle waveform proves to be far superior upon completion of the experiments, this waveform will be identified as optimal barring significant side-effects. However, if the other waveforms provide equivalent efficacy at comparable power levels, stimulus formats using shorter pulse durations will be selected as optimal due to concommitant reductions in iontophoresis associated with each EA stimulus pulse.

In addition to marked effectiveness during EA, the data indicates dramatic post-EA effects for all duty cycles. Similar post-stimulation analgesia has been noted in association with TNS investigations in general somatic (non-orofacial) anatomical fields, and was also a characteristic feature noted in our prior human studies using experimental orofacial pain (34). Neurological mechanisms subserving this phenomenon are unidentified, but since the present studies involved EA stimulation in a dermatome (Trigeminal III) distinct from the origin of pain (Trigeminal II), the effects are almost certainly dependent on interactions in the central nervous system. The observed post-EA analgesia could have profound clinical significance if sufficient efficacy can be obtained, as pre-operative or "waiting room" analgesia may prove to be feasible.

Significant attrition has occurred in conducting animals through the several stages of surgery and training to finally permit collection of Threshold Titration data with accompanying EA. Also, the Threshold Titration data showed a significant amount of variability, as the animals exhibited a wide range of responses around the mean tolerance level within the control, EA, and post-EA periods. Nevertheless, the data indicate that, given a sufficient number of stimulus trials within each experiment, the experimental model is quite adequate to provide a quantitative measure of average tolerance levels and changes therein induced by the application of EA. The Chronic Psychophysiological model is presently fully operational and on-line, and will provide a powerful tool for the development of EA techniques and the production of safety documentation.

RECEPTOR BLOCK ELECTROANALGESIA: ACUTE NEUROPHYSIOLOGICAL INVESTIGATIONS

Contemporary investigations related to Receptor Block EA have almost exclusively involved human experiments related to one of three techniques used in clinical dentistry, vitalometry, electroanalgesia, and desensitization.

Vitalometry involves the application of alternating current waveforms to intact teeth to determine the minimum stimulus intensity necessary for perceptual experience. The latter knowledge can be related in a complicated way to the health status of the pulp (68). Vitalometric techniques are apparently innocuous, do not involve analgesia, and therefore have little relevance to Receptor Block EA except to the extent that they contribute to the understanding of pulpal sensibility.

Some reports related to dental electroanalgesia appeared in the 1950's and 1960's, but the results were generally inconclusive (35). A few studies involved the use of alternating current waveforms (35), thereby theoretically reducing contingencies related to current-induced irreversible effects. The alternating current intensities did not exceed several microamperes, and only incomplete success was obtained under the most favorable of circumstances. Most studies used a direct waveform ranging to 60 μA (35). Results using these higher levels of direct current indicated a complete block of perceptual and reflex manifestations of afferent activity (35,63,69), and analogous results have been found in studies of peripheral nerve conduction. Lower intensities of direct current exhibited varying degrees of success or failure (35). It is important to note that while patients were apparently asymptomatic in their post-treatment histories (35), our studies have demonstrated that such stimulation induces definite irreversible effects on pulpal excitability (56,58).

Direct currents ranging to several mA are routinely used for dental desensitization procedures (35). The latter techniques produce permanent damage and tissue alterations, in that significant formation of reparative dentin and dead tracks is introduced, in spite of apparent asymptomatic post-treatment histories (35). Based upon the data from our laboratory (56,58), the irreversible consequences of such stimulation would render proposals for even its preliminary study unacceptable in the context of present requirements for institutional Human Rights approval. It is this very contingency of such drastic irreversibility that we are seeking to alleviate.

The above information conclusively demonstrates that electrical currents are capable of inducing a complete block of pulp-elicited afferent activity under the general heading of Receptor Block EA as presently defined. However, the traditional clinical techniques are either highly suspect or blatantly guilty of inducing prolonged or permanent functional alterations of structural integrity, a conclusion following directly from our previous data (56,58).

The use of intermittent waveforms (pulsating direct current or alternating current) for the induction of Receptor Block EA, which we originally proposed and on which our present program is based (34,56), is the only viable solution to this dilemma that has been proposed. We reasoned conceptually and subsequently established experimentally that a substantial reduction of total power transfer afforded by intermittent waveforms as opposed to continuous direct current might permit the retention of analgesia while simultaneously reducing the irreversible consequences of EA stimulation. For complicated reasons discussed previously (34), the investigation of intermittent EA waveforms required recordings from single pulp driven units in the Gasserian ganglion, and development of the ganglionic recording model was completed just prior to the present contractural period. The work of the present contract year involved the final verification of Receptor Block EA feasibility and the characterization of the optimal duty cycle and frequency of pulsating direct current EA.

Methods

Animal Preparation. Eighty-six young adult cats weighing 2-4 kg were used in the present studies, with a complete complement of quantitative data obtained in 44 experiments. The animals were anesthetized with sodium pentobarbital, and a Bird Mark IV-VIII provided automatic artificial ventilation if necessary (rarely activated). Esophogeal temperature, systolic and diastolic blood pressure, and end-tidal CO_2 were monitored and maintained as described previously (55,56,58,59).

Stimulation. The tooth preparation was carefully designed to minimize disturbances of the pulpal environment, to maximize electrode area and minimize polarization, and to insure confinement of stimuli to the test pulp (37,38,40,41).

Test stimuli were applied to a maxillary canine tooth pulp using platinum electrodes placed in two shallow cavities just through the enamel. The two non-occlusal electrodes thereby formed were used for the application of test stimuli, the latter being monophasic rectangular pulses of an intensity appropriate to the particular test. Test stimuli were derived from a specially designed battery-powered, photically-isolated constant-current stimulator driven by one channel of a Grass S-88 physiological stimulator. To permit test stimulation free from artifact, the EA stimulus train (described below) was interrupted for a period of 30 msec at 200 msec intervals, and the test stimulus was presented 15 msec after each interruption of EA.

The EA electrode contact was formed by removing the occlusal one-third of the test tooth enamel and immersing the exposed dentin in a plexiglas cup containing normal saline and a platinum electrode. The monopolar stimulus configuration was used for the application of EA current, using the occlusal cup electrode referenced to a 1 cm length of platinum wire inserted subcutaneously in the contralateral cheek. EA currents were trains of monophasic rectangular pulses of anodal polarity at the occlusal cup electrode. A

calibration curve for EA current related the voltage output of a Hewlett-Packard Model 8011A pulse generator and the output of the current generator described below.

EA and test stimulus intensities were recorded in terms of current. Certain precautions related to such measurements and the relationship of current to other electrical parameters have been previously discussed (59). A new isolated-output constant-current generator has recently been designed and fabricated in our laboratory. The latter device incorporates state-of-the-art features to absolutely minimize current leakage between stimulation lead wires, which occurs by virtue of capacitive reactance pathways available to high-frequency components of the EA stimulus train. The output characteristics of the stimulator and its experimental positioning reduced such current leakage problems to negligible values (less than one percent). Thus, all reported EA currents arrived at the electrode-tissue interface and therefore passed through the biological tissue of interest, with the exception of any currents involved in charge storage associated with polarization of the stimulating electrodes (59). The stimulator had a measured rise-time of less than 10 ns in the experimental situation.

Recording. The anesthetized animal was mounted in a stereotaxic apparatus (Model 1504, David Kopf Instruments). Cranial musculature was reflected, a parieto-temporal craniotomy was performed, cerebral tissue was removed to expose the Gasserian ganglion, and the ganglion was thereafter placed under mineral oil maintained at 38 $\pm$ 0.5 C. All recordings involved Frederick Haer epoxy-coated tungsten microelectrodes, using penetrations oriented perpendicular to the horizontal stereotaxic plane. The recording electrode was connected to a Frederick Haer d-c Preamplifier Model 40-20-2, and from there to a 60 Hz notch filter (Mentor Model F-60), a bandpass-limited amplifier (Tektronix Model 3A9), and an oscilloscope (Tektronix 564-B).

Experimental Protocols. Three distinct experimental protocols were completed in the present contract year, being a preliminary feasibility study, a duty cycle series, and a frequency series, respectively. The purpose of the preliminary series was to investigate the feasibility of using intermittent Receptor Block EA waveforms, by surveying several intermittent rectangular pulse trains having various frequencies and duty cycles and comparing the efficacy of block to that of continuous direct current. The purpose of the duty cycle series was to identify the optimal duty cycle of Receptor Block EA, and the last experimental series served to identify the optimal frequency of Receptor Block EA, using the duty cycle identified in the previous experiments. All three experimental series involved identical details regarding the format of data collection, described in detail below.

Exploration of the Gasserian ganglion ipsilateral to the test tooth involved electrode penetrations in a rostrocaudal and mediolateral grid of 0.5 mm steps and at frequent subsurface depths to identify responses elicited by supramaximal stimulation of the test tooth (200 μA, 0.1 msec). Cautious attempts were made to maximize response amplitude of identified pulp-driven

units by further vertical movements of the recording electrode. Subsequently, physiological characteristics of the pulp-driven unit were characterized for a comparison with previous results (59).

Definitive protocols were composed of successive EA intensity-stepping series using a particular continuous train of monophasic rectangular pulses. In each EA intensity-stepping series, the threshold of a pulp-driven unit was recorded every 15 sec while peak EA intensity was varied in step increments of 10 μA in an ascending series from 0-100 μA. Each level of EA intensity was maintained for one minute. Within an individual experiment, successive EA intensity-stepping series were without exception conducted in the order of lowest to highest power transfer, if applicable, and prolonged time intervals separated individual intensity-stepping series to minimize accumulative effects (56,58,59,63). The preliminary experimental series involved a survey of the effectiveness of waveforms having various combinations of 10 pps, 100 pps and 1000 pps frequency and duty cycles of 1% and 10%. The duty cycle series investigated values of 1.00%, 3.16%, and 10.0% (equally spaced logarithmically) at a frequency of 1000 pps, a range of values identified as optimal in the preliminary series (59). The frequency series involved characterization of the efficacy of 100 pps, 1000 pps, 10,000 pps and 100,000 pps, using a duty cycle of 10% identified as the most effective in the previous duty cycle series. Experiments were usually terminated with an intensity-stepping series involving continuous direct current for comparison with previous data (59). Following each EA intensity-stepping episode, recordings were continued for varying periods to document recovery.

Results

Preliminary Experimental Series. Figure 1 summarizes data from 12 experiments in which the EA intensity-stepping series was administered to a test tooth while the thresholds of single pulp-driven units in the Gasserian ganglion were monitored. In some experiments an initial slight hyperexcitability was found at low levels of constant direct current EA, as evident in the averaged data of Figure 1. As the level of constant direct current EA was increased, a marked progressive hypoexcitability was evident which finally reached a plateau at an EA intensity of 70-80 μA. The two 10 Hz pulsating waveforms (1 and 10% duty cycles, respectively) elicited negligible alterations of thresholds for all levels of EA ranging to 100 μA. Using the 100 Hz pulsating waveforms, the 1% duty cycle tests resulted in a progressive elevation in threshold which eventually reached a value of approximately 37% of the effectiveness of constant direct current EA at 100 μA, whereas the 10% duty cycle tests resulted in a qualitatively similar response pattern which was 58% as effective as constant direct current EA at 100 μA. Finally, the 1000 Hz pulsating waveform (examined at a 10% duty cycle only) exhibited approximately 90% of the efficacy of constant direct current EA at 100 μA, and actually exceeded the effectiveness of constant direct current for certain intermediate EA intensities. Both the pulsating and constant direct current waveforms exhibited initial elevations from control levels at approximately 20 to 30 μA, progressively rose with EA intensities in the range of 30 to 100 μA, and in some cases, the thresholds tended to reach a plateau at EA intensities above 70 to 80 μA.

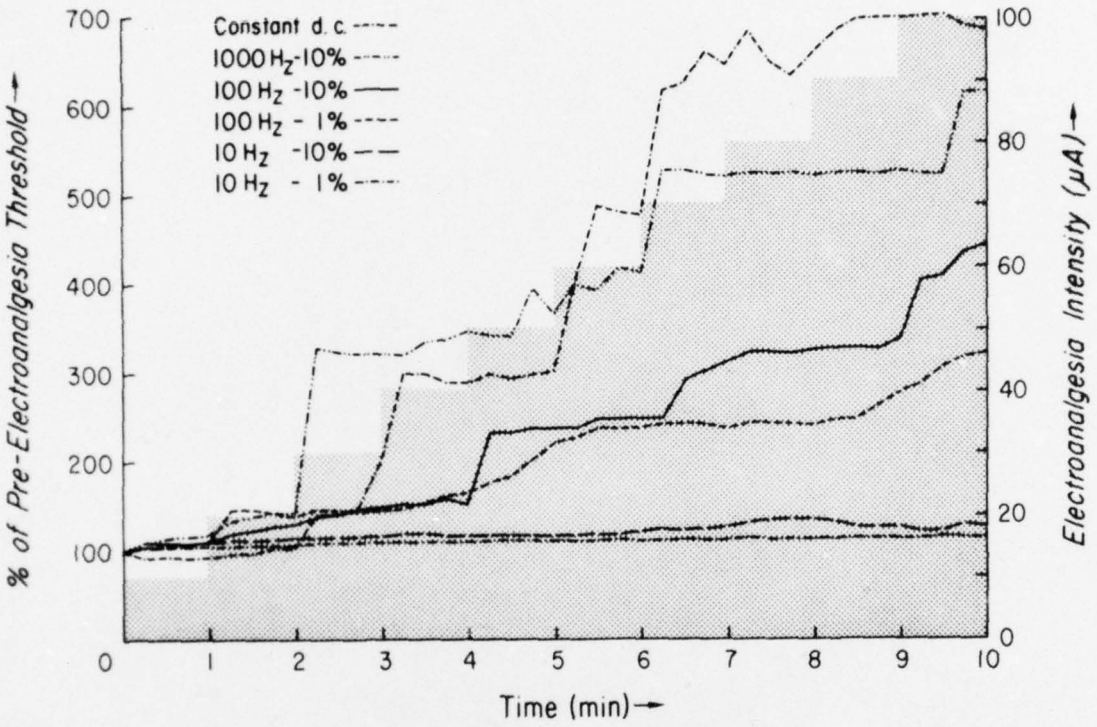

Figure 1. Averaged Data of the Relative Threshold of Single Pulp-Driven Ganglionic Units During EA Intensity-Stepping Series; Preliminary Experimental Series (N=12). Thresholds of each individual unit were normalized by comparison to average values prior to initiation of electroanalgesia. All data points in each series were recorded at 15 sec intervals. Left ordinate (% of control threshold) refers to data curves; right ordinate (electroanalgesia intensity) refers to the shadowed background.

The results using the various EA waveforms have been quantitatively analyzed using the repeated analysis of variance procedure to compare maximal levels of threshold elevation which were achieved. For each waveform, all threshold readings taken for EA current levels of 80 to 100 μA were combined, as the averaged results of the constant direct current tests in this range showed a marked tendency to reach a plateau. The results, presented in Table VIII, indicate that both intensity and waveform, considered individually, were s tistically significant variables in terms of the efficacy of EA, although no interaction between these two variables was revealed. Further analysis using Duncan's Multiple Range Test indicated no significant differences in threshold elevation between the 80 μA and 90 μA EA current intensities, but both of the latter intensities were significantly less efficacious than 100 μA EA ($p < 0.05$). The most effective pulsating direct current waveform (1000 Hz-10% duty cycle) did not differ significantly from constant direct current in the range of intensities subjected to statistical analysis, although all other pulsating direct current waveforms were significantly different from constant direct current (these conclusions were based on the 0.05 level of statistical probability). Using the same statistical criteria, the 1000 Hz-10% waveform differed significantly from all other pulsating direct current waveforms except that of the 100 Hz-10% duty cycle. Extending the above analysis, the 100 Hz-1% waveform did not differ significantly from either 10 Hz waveform based on the number of experiments analyzed, in spite of visual impressions to the contrary exhibited by the averaged data of Figure 1.

The time course of recovery from EA current is summarized in Figure 2. The constant direct current waveform, again used as the basis for comparison with our previous work (56,58), displayed a partial diminution of hypoexcitability during the first minute. However, this intermediate elevated threshold value was thereafter retained, there being no further tendency for recovery of pre-EA levels of excitability over the post-EA interval examined. This behavior is analogous to our previous field-potential characterizations in the trigeminal complex of the brain stem (56). In contrast, with all pulsating direct current waveforms, the threshold fell to much lower values within the first minute, and, subsequently, displayed a progressive tendency to further approach pre-EA levels in the succeeding minutes. In the present experiments, the recovery period was not followed for extended periods of time, in favor of collecting complete EA data sets involving a greater number of independent waveforms.

Duty Cycle Experimental Series. Figure 3 summarizes the results of 16 experiments in which a complete set of EA intensity-stepping series data was obtained for all three duty cycles of interest. In seven of the 16 experiments, an intensity-stepping series involving continuous direct current EA (100% duty cycle) constituted an additional final episode.

An initial slight hyperexcitability was observed in most constant direct current intensity-stepping series at low levels of EA (Figure 3), confirming previous observations (59). The primary EA effect was a marked progressive hypoexcitability prominent at intermediate levels of EA but then reaching

TABLE VIII

Relative Waveform Effectiveness in the Preliminary Experimental Series

Source	SS	df	MS	F	P
Total	27,072,039	161			
Animals	8,052,396	8			
Waveform	8,743,446	5	1,748,689	7.41	< 0.001
Intensity	63,305	2	32,152	4.76	< 0.025
Waveform X intensity	65,924	10	6,592	0.89	> 0.050
Error (waveform)	9,443,849	40	236,096		
Error (intensity)	107,968	16	6,748		
Error (intensity X intensity)	594,152	80	7,427		

Repeated measures analysis of variance of pulpal threshold values during 80 to 100 μA electroanalgesia. For this analysis, it was necessary to reduce the experimental N from 12 to nine due to the absence of values from particular electroanalgesia intensity-waveform conditions.

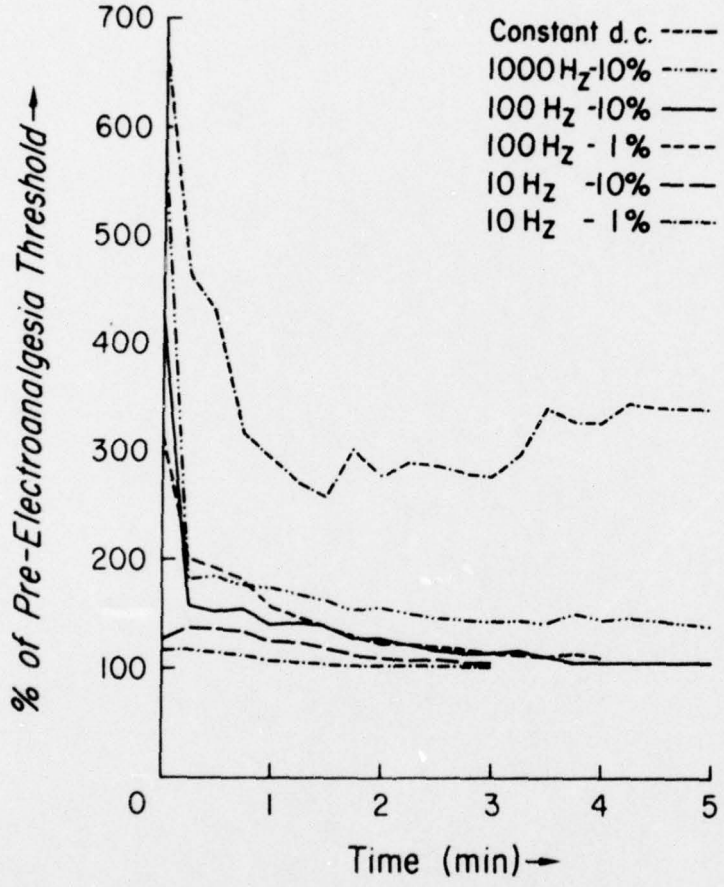

Figure 2. Averaged Data of the Relative Threshold of Single Pulp-Driven Ganglionic Units Following EA Intensity-Stepping Series; Preliminary Experimental Series (N=12). Thresholds of each individual unit were normalized by comparison to its average values prior to initiation of electroanalgesia.

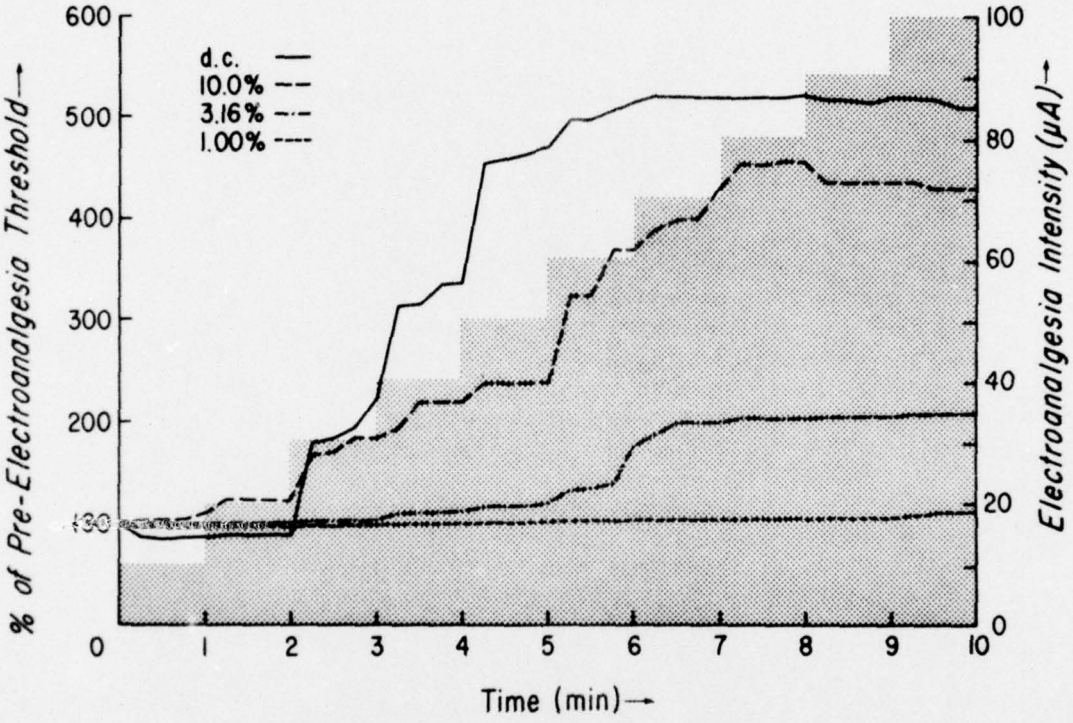

Figure 3. Averaged Data of the Relative Threshold of Single Pulp-Driven Ganglionic Units During EA Intensity-Stepping Series; Duty Cycle Experimental Series. N=16 for pulsating waveforms and 7 for the continuous direct current. Thresholds of each individual unit were normalized by comparison to its averaged value prior to the initiation of electroanalgesia. All data points in each series were recorded at 15 sec intervals. Left ordinate (% of control threshold) refers to data curves; right ordinate (electroanalgesia intensity) refers to the shadowed background.

maximal effectiveness at the higher intensities investigated. The averaged results for all effective duty cycles were similar in general features, but the magnitude of effects were strongly duty cycle dependent. Hypoexcitability was essentially absent for low EA intensities ($<$ 20 μA), then became positively correlated with EA intensity for intermediate values (approximately 20-70 μA), and then reached maximal levels for the higher EA intensities studied ($>$ 70 uA). The 1.00% duty cycle waveform lacked effectiveness at all EA intensities investigated. With the 3.16% duty cycle, noticeable effects were not apparent until intensity levels of 50-60 μA, and did not exceed a two fold increase in threshold at EA intensities of 70-100 μA. The 10.0% duty cycle and direct current (100% duty cycle) waveforms exhibited a pronounced positive dependence of hypoexcitability on EA intensity in the range of approximately 20-70 μA, at which point the effectiveness became independent of further increases in EA magnitude. Maximal increases in threshold for the 10.0% and direct current waveforms were in the range of 400-500% of control values.

The data characterizing the efficacy of various EA duty cycles was quantitatively analyzed using a factorial analysis of variance (70) to compare maximum threshold elevations. The results of the analysis are summarized in Table IX. Neither the interaction between duty cycle and intensity nor the main effect for intensity approached significance ($p > .10$). The absence of an effect for intensity indicates a marked tendency of EA to reach maximal effectiveness in the range of 70-100 μA (the effects plateaued). The plateauing phenomena is evident to visual inspection of the data of Figure 3 and has also been noted in a previous study (59). The main effect for duty cycle was significant ($p < .05$). A Schaffes test (70) was then performed to determine the differences in effectiveness for the various duty cycles within the range of 70-100 μA EA. The Schaffes test indicated that the 1.00% and 3.16% duty cycle conditions were not distinguishable from each other, but both of the latter waveforms were significantly less effective than the 10.0% duty cycle and direct current EA. There was no significant difference between the effectiveness of the 10.0% duty cycle and continuous direct current.

The temporal course of the averaged pulpal threshold data which occurred during post-EA recovery periods is shown in Figure 4. The data indicates that following termination of all EA waveforms studied, pulpal excitability returned to near control levels after 1-2 min with one exception. The temporal profile of the 10.0% duty cycle data indicated a slight delay in recovery when compared to the other waveforms, although recovery was essentially complete eight minutes following termination of EA. The latter time course is similar to that observed for the same waveform in the preliminary study (59).

The time course of averaged pulpal thresholds following direct current EA was somewhat unexpected in that normal excitability was so rapidly achieved, although the number of experiments contributing to these results was small in number (seven of sixteen). Previous averaged results involving continuous direct current EA recorded under similar (41) or somewhat differing (40) circumstances indicated a significant degree of post-EA hypoexcitability.

TABLE IX

Relative Waveform Effectiveness in the Duty Cycle Experimental Series

Source	SS	df	MS	F	P
Total	22,145,206	219			
Duty cycle	5,424,952	3	1,808,317	22.10	$p < .05$
Intensity	9,018	3	3,006	0.04	$p > .10$
Duty cycle X intensity	16,182	9	1,798	0.02	$p > .10$
Error	16,695,054	204	81,839		

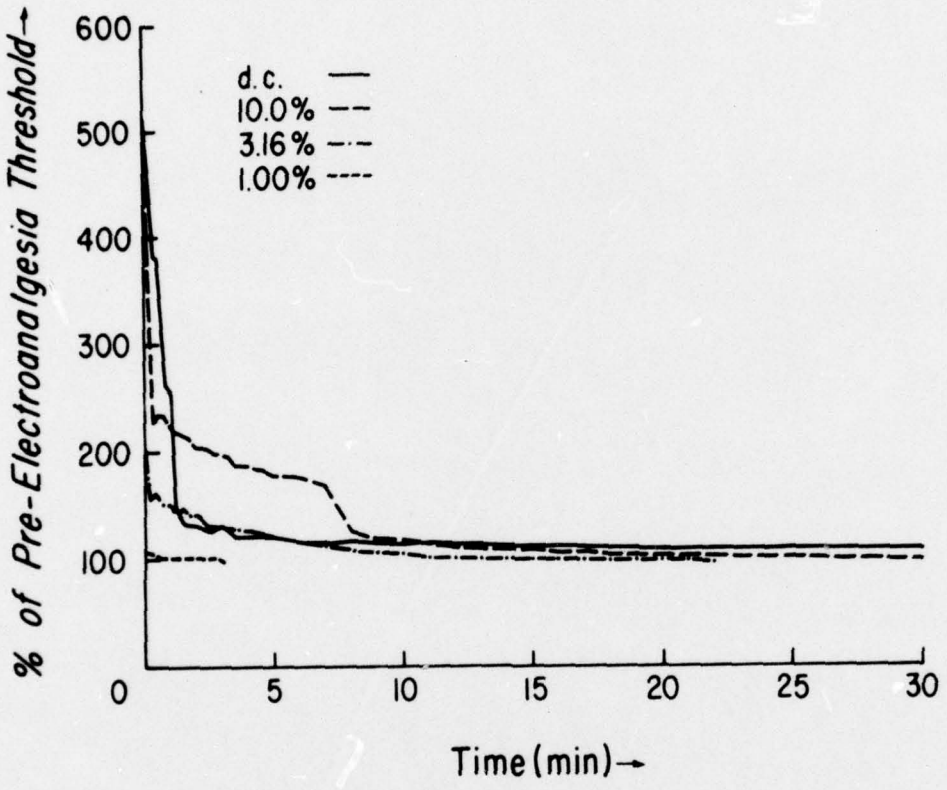

Figure 4. Averaged Data of the Relative Threshold of Single Pulp-Driven Ganglionic Units Following EA Intensity-Stepping Series; Duty Cycle Experimental Series. N=16 for pulsating waveforms and 7 for the continuous direct current. Thresholds of each individual unit were normalized by comparison to its averaged value prior to the initiation of electroanalgesia. All data points were collected at 15 sec intervals for the first five minutes following the termination of electroanalgesia and every one minute thereafter. Threshold recordings were discontinued when control values were attained.

In this context, it is important to note that the raw data from an individual unit during recovery as well as during EA was typically quite uniform but there was considerable variability between individual units. Similar variability has also been reported by other workers (50). If a total block is defined as a threshold elevation in excess of ten times the control value and recovery as a return to within 25% of control excitability, then the primary afferents observed to date can be assigned to one of two categories. Combining previous (59) direct current EA data with the analogous data from the present investigation, all fibers (eight) which were not totally blocked exhibited recovery, whereas approximately half (four of nine) of the fibers which were totally blocked did not recover within the post-EA period of measurement. These results are not apparent in the averaged data of Figure 4, because in the present experiments fewer direct current EA stepping series were included and of those completed only one of three fibers which underwent total block failed to recover.

Frequency Experimental Series. Figure 5 summarizes the results of 16 experiments in which a complete set of EA intensity-stepping series data was obtained for all four pulsating direct current frequencies of interest as well as a continuous direct current series for comparison. An initial hyperexcitability was observed in most constant direct current intensity-stepping series at low levels of EA current (Figure 5), confirming previous observations (59). For effective waveforms, the primary EA effect was a marked progressive hypoexcitability prominent at intermediate and high levels of EA, the effects being slightly concave to the time (EA intensity) axis. EA efficacy was strongly dependent on frequency and EA intensity. Hypoexcitability was essentially absent for low EA intensities (< 20 μA) for all intermittent pulse trains except the 100 pps waveform, then became positively correlated with EA intensity for intermediate values (approximately 20-70 μA), and in most instances, the effectiveness plateaued for higher EA intensities investigated (> 70 μA). The 10,000 pps and 100,000 pps waveforms showed little effect at any of the EA intensities investigated. With the 100 pps waveform, the effects gradually rose to a level of 150% of control for intermediate and high intensities and showed a large increase to 200% of control thresholds above 90 μA. The latter increase was essentially due to an enormous increase observed in two experimental animals, and the remaining units exhibited the plateau phenomenon. The 1000 pps frequency and the direct current waveform exhibited a pronounced positive dependence of hypoexcitability on EA intensity for intermediate and high levels of EA stimulation. Maximal increases in threshold for the 1000 pps and direct current waveforms were approximately 400% of control values.

Changes in pulpal unit thresholds were analyzed with the Repeated Measures Analysis of Variance. For each waveform, all threshold readings for EA currents of 70-100 μA were combined, as in the previous experimental series, to further examine the plateauing phenomenon. The main effects for both intensity and frequency were significant ($p < .05$; $p < .05$, respectively), but the interaction between intensity and frequency did not attain significance ($p > .05$). Therefore, Duncan's Multiple Range Test for Mean Difference was calculated for both the different levels of EA intensity and the different

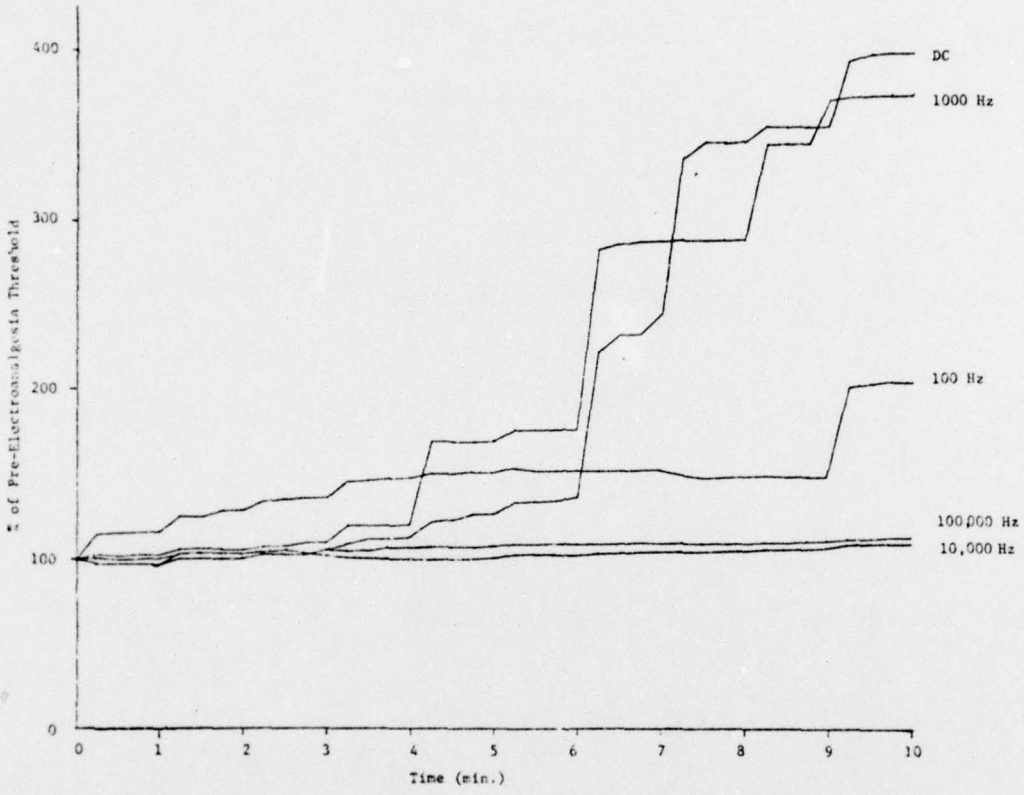

Figure 5. Averaged Data of the Relative Threshold of Single Pulp-Driven Ganglionic Units During EA Intensity-Stepping Series; Frequency Experimental Series. N=16 for all waveforms examined. Thresholds of each individual unit were normalized by comparison to its averaged value prior to the initiation of electroanalgesia. All data points in each series were recorded at 15 sec intervals. Left ordinate (% of control threshold) refers to data curves; right ordinate (electroanalgesia intensity) refers to the shadowed background.

EA waveform frequencies. The 70 μA condition demonstrated the least threshold elevation. The 80 and 90 μA conditions both were superior to the 70 μA condition but did not differ within themselves. The 100 μA condition proved to be the most effective of all four intensity levels. In examining the different frequencies, it was found that the 100, 10,000, and 100,000 pps conditions demonstrated statistically similar and minimal influences on pulpal thresholds. In contrast, both the 1000 pps and continuous direct current conditions generated a significant threshold elevation which was statistically indistinguishable. Table X summarizes the analysis.

The main effect for intensity was somewhat surprising since it has not appeared in previous analyses. A consideration of the statistical validity of this finding therefore seemed worthy of attention. The threshold increment was most unexpected at the 100 μA level. The 100 pps, 1000 pps, and continuous direct current conditions all exhibited distinct threshold increases at this intensity level. In returning to the raw threshold elevation data, the data of two animals stood glaringly apart from that of the others. Animal # 1 had a rather unusual pattern of threshold change in the 100 Hz condition. While the animal showed a threshold elevation of only 10% over control through 90 μA, it suddenly was elevated to more than 800% over control during 100 μA. Animal # 12 had a similar sudden shift in the 1000 Hz condition where in the last 15 seconds of the 90 μA level, its unit's threshold jumped from 78% over control to more than 800% over control. These very large threshold shifts may have been the sole basis for the main effect for intensity which the statistical analysis suggested. In order to test the latter supposition, the data of these two animals were excluded and a reanalysis was performed. In this analysis there was a significant interaction between intensity and frequency [$F=3.25$, $d.f.=(12,156)$, $p < .05$]. This interaction reflected the single instance in which an effect for intensity still was present, it being a difference between the 70 μA and 80 μA conditions for the continuous direct current condition. No other intensity comparisons yielded a significant difference.

There exists an excellent a priori reason to exclude the data of these two animals. The temporal threshold profile described above is obviously reminiscent of the 'irreversible threshold' phenomenon which we have previously identified (58). Therefore, after excluding the aberrant data involving the distinct physiological phenomenon of irreversibility, the present data further confirms the plateau phenomenon in the range of 80-100 μA EA. Data from the duty cycle experiments also indicated plateauing was manifest at 70 μA, but the phenomenon was not evident in the frequency or the preliminary experimental series until 80 μA.

The temporal course of the average pulpal threshold data which occurred during post-EA recovery periods is shown in Figure 6. The data indicates that following the termination of 100 pps, 10,000 pps, and 100,000 pps EA, pulpal excitability returned to near control levels after, at most, seven minutes. The temporal profile of the 1000 pps data indicated a slight delay in recovery when compared to the abovementioned waveforms, although recovery was essentially complete twelve minutes following EA termination. The continuous direct

TABLE X

Relative Waveform Effectiveness in the Frequency Experimental Series

Source	SS	df	MS	F	P
Total	17,735,063.5	319			
Animals	4,679,102.7	15			
Intensity	163,628.4	3	54,542.8	15.1	< .05
Frequency	3,199,740.1	4	799,935.0	6.4	< .05
Intensity X frequency	193,735.6	12	16,144.6	1.6	> .05 n.s.
Error intensity	163,059.4	45	3,623.5		
Error frequency	7,471,913.6	60	124,531.9		
Error intensity X frequency	1,863,883.7	180	10,354.9		

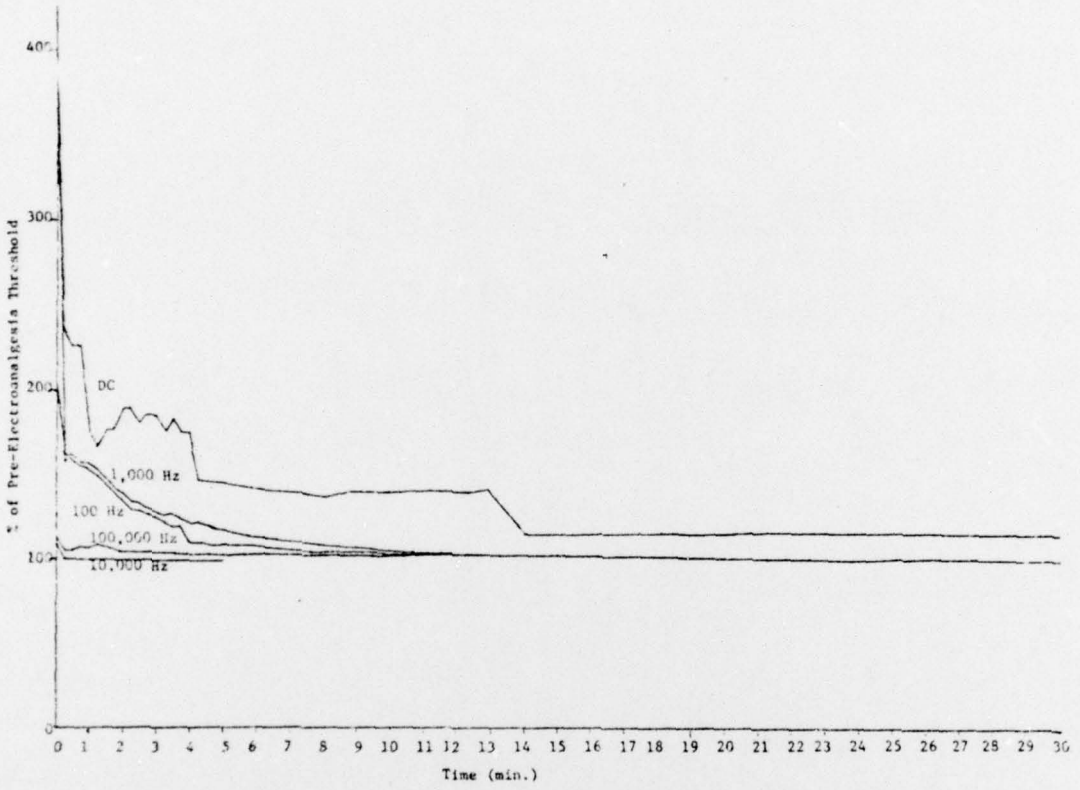

Figure 6. Averaged Data of the Relative Threshold of Single Pulp-Driven Ganglionic Units Following EA Intensity-Stepping Series; Frequency Experimental Series. N=16 for all waveforms examined. Thresholds of each individual unit were normalized by comparison to its averaged value prior to the initiation of electroanalgesia. All data points were collected at 15 sec intervals for the first five minutes following the termination of electroanalgesia and every one minute thereafter. Threshold recordings were discontinued when control values were attained.

current data showed an even more prolonged post-EA hypoexcitability and never did completely recover during the observation interval. It is important to note that the duration of EA administration using the present experimental format is very short, including only several minutes at the higher EA intensities. Preliminary data in association with another study in our laboratory indicates that continuous direct current stimulation maintained for longer periods results in pronounced irreversibility.

Discussion

The present results establish the feasibility of pulsating direct current EA. The optimal waveform based on the data to date is composed of a train of monophasic anodal rectangular pulses of 10% duty cycle and frequency of 1000 pps. At comparable peak intensities (and therefore only 10% of the electrical power), the latter waveform produced blockades of pulpal afferent activity statistically indistinguishable from continuous direct current EA. Reductions in duty cycle below 10% or the use of frequencies above or below 1000 pps produced a pronounced roll-off in EA efficacy.

Data from the duty cycle series indicated an absence of a main effect for intensity in the statistical analysis of the data ranging from 70-100 μA, indicating the presence of a plateau effect in this range for all duty cycles investigated. A strong tendency toward the plateau effect was also noted in the preliminary series and also in the frequency series if the data of two units is omitted. Perusal of the raw data from individual experiments indicates that most units tend to show a definite plateauing effect in the range of 70-100 μA, but the results are less conclusive in some of the averaged data due to the pronounced effect of a small number of units exhibiting wildly aberrant behavior. The nature of the aberrant behavior is a sudden and seemingly irreversible enormous increase in threshold such that the units cannot be activated at all, apparently the result of exceeding the 'irreversibility threshold' which we have previously described (58). It appears that the plateau phenomenon is real, but its presence in the average data is obscured by occasional interference of the 'irreversibility' phenomenon. The data is presently being reanalyzed to properly distinguish conclusions following appropriate consideration of both the 'plateau' and 'irreversibility' phenomena.

Results in the Receptor Block program to date are profoundly significant clinically. The data indicates that the use of a continuous train of rectangular anodal pulses (a pulsating direct current waveform) of 10% duty cycle and 1000 pps frequency permits retention of analgesia while affording an order of magnitude reduction in power and negligible irreversibility contingencies, when compared to continuous direct current EA. Experiments scheduled for the immediate future will test the efficacy of alternating current waveforms, desirous because of decreased iontophoresis, and to verify Receptor Block EA at the perceptual level in Chronic experiments.

GATING BLOCK EA: HUMAN PSYCHOPHYSIOLOGICAL EXPERIMENTS

A. The Human work of the present contract year was composed of two distinct phases, Phase I and Phase II, both involving the use of experimental pain (electrical pulp stimulation; a second, independent stimulus channel).

B. The Phase I studies were directed to a preliminary survey of particular electrode configurations and sites of stimulation:

   a) The use of two or three active EA electrodes were ineffective when compared to the use of one active electrode (all electrodes having identical area) using comparable current densities. Therefore, only one active electrode (4 mm X 4 mm) will be used in a general region of stimulation.

   b) Four orofacial anatomical stimulus sites were examined in detail. The two most effective sites were the Mental Foramen and our standard Intraoral Mucosa site near the test tooth which we have used historically. The Infraorbital Foramen and Intraoral Salivary Duct sites proved to be unsatisfactory.

C. The Phase II studies were composed of a quantitative comparison of the Mental Foramen versus the Intraoral Mucosa sites identified as the most effective in the Phase I work. This is an important consideration because the Mental Foramen site is much more accessible.

   a) Stimulation of both sites resulted in reduced pain responsiveness in virtually <u>every</u> test stimulus <u>trial</u> after induction. Intermediate stages of induction were not as rapid using the Mental Foramen site.

   b) Stimulation of the Mental Foramen site produced equivalent or superior reductions in pain responsiveness judged by the magnitude of the <u>sensory category shift</u>. Intermediate stages of induction were not as rapid using the Mental Foramen site.

   c) It was concluded that the Mental Foramen site can be substituted for the Intraoral Mucosa site at the present stage of technique development. Future work will permit better understanding and hopefully significant improvements in EA induction.

GATING BLOCK EA: CHRONIC PSYCHOPHYSIOLOGICAL EXPERIMENTS

A. The work of the present contract year involved the final development of the Chronic experimental model and the initiation of the first definitive experimental series testing EA.

The Chronic model features pulp stimulation through implanted electrodes as the source of pain, the application of EA through separately implanted electrodes, the use of an acrylic head pedestal for animal-equipment communications, the use of Automatic Shaping procedures for animal training, and the long-term monitoring of pulpal stimulation tolerance using the Threshold Titration paradigm of experimental psychology.

a) The complicated series of training paradigms (Footshock, Pulp-shock, and Threshold Titration are described in their fully developed form, and the nature of the Chronic model is quantitatively characterized.

b) During the present contract year the entire Automatic Shaping facility was placed under the control of a microcomputer system, greatly increasing the reliability compared to previous antiquated apparatus.

C. The first definitive EA experimental series has recently been initiated, directed to a survey of duty cycles using our standard stimulation frequency and waveform (100 pps bidirectional rectangular pulse train) from prior human work.

a) To date, the data from twenty experiments has been analyzed. The results show that the EA stimulation dramatically increases the tolerance to pulp stimulation.

b) The present data suggests that a large duty cycle of 31.6% may prove to be somewhat superior to duty cycles of 10.0% and 3.16%, although the experimental N is too small for definitive conclusions at present.

RECEPTOR BLOCK EA: ACUTE NEUROPHYSIOLOGICAL EXPERIMENTS

A. The Acute experiments of the present contract year involved three independent series, a preliminary series to test the concept of pulsating direct current Receptor Block EA, a series to identify the optimal duty cycle, and a series to identify the optimal frequency.

   a) The conduct of the latter two series required the design and fabrication of a sophisticated high-frequency isolated pulse generator.

   b) The preliminary series demonstrated conclusively that the pulsating direct current waveform permitted retention of analgesia while virtually eliminating post-EA irreversibility, indicating the significance of duty cycle and frequency for subsequent study.

   c) The duty cycle series established that 10.0% was the optimal duty cycle, as that value produced an afferent blockade indistinguishable from continuous direct current. Duty cycles of 3.16% and 1.00% were less and less effective, respectively. Irreversibility problems were not manifest following termination of the pulsating EA.

   d) The frequency series established that the optimal frequency in the range of 100 pps to 100,000 pps examined is approximately 1000 pps. This result is unexpected and profound because it lies above the normal physiological range for pulpal fibers and far below the value used by Limoge.

LITERATURE CITED

1. Melzack, R. and Wall, P.D. (1965). Pain mechanisms: a new theory. Science 150: 971-979.

2. Casey, K.L. (1973). Pain: a current view of neural mechanisms. Amer. Scientist. 61: 194-200.

3. Burgess, P.R. (1974). The physiology of pain. Amer. J. Chin. Med. 2: 121-148.

4. Melzack, R. and Wall, P.D. (1970). Psychophysiology of pain. In: H. Yamamura, Editor. Anesthesia and Neurophysiology. International Anesthesiology Clinics, Little, Brown and Company. Boston, Mass. 8(1): 3-34.

5. Taub, A. (1975). Electrical stimulation for the relief of pain: two lessons in teleological zealotry. Perspect. Biol. Med. 19: 125-135.

6. Kirkpatrick, D.B. and Kruger, L. (1975). Physiological properties of neurons in the principal sensory trigeminal nucleus of the cat. Exp. Neurol. 48: 664-690.

7. Yu, Y.J. and King, R.B. (1974). Trigeminal main sensory nucleus polymodal unit responses to noxious and non-noxious stimuli. Brain Res. 72: 147-152.

8. Kruger, L. and Mosso, J.A. (1974). An evaluation of duality in the trigeminal afferent system. In: J.J. Bonica, Editor: Advances in Neurology, Vol. 4. Pain. Raven Press. New York. pp. 73-82.

9. Bowsher, D. (1974). Thalamic convergence and divergence of information generated by noxious stimulation. In: J.J. Bonica, Editor: Advances in Neurology, Vol. 4. Pain. Raven Press. New York. pp. 223-232.

10. Casey, K.L., Keene, J.J. and Morrow, T. (1974). Bulboreticular and medial thalamic unit activity in relation to aversive behavior and pain. In: J.J. Bonica, Editor: Advances in Neurology, Vol. 4. Pain. Raven Press. New York. pp. 197-205.

11. Emmers, R. and Ruderman, M.I. (1974). Inhibition at the T-cells of the spinothalamic tract: a neurophysiological basis for electrically induced analgesia. Proc. Soc. Exptl. Biol. Med. 145: 1310-1316.

12. Sessle, B.J. and Greenwood, F. (1974). Influence of trigeminal nucleus caudalis on the responses of cat trigeminal brain stem neurones with orofacial mechanoreceptive fields. Brain Res. 67: 330-333.

13. Khayyat, G.F., Yu, Y.J. and King, R.B. (1975). Response patterns to noxious and non-noxious stimuli in rostral trigeminal relay nuclei. Brain Res. 97: 47-60.

14. Young, R.F. and Nord, S.G. (1975). Experimental modulation of medullary dental pulp units by mechanical stimulation of orofacial fields. Exp. Neurol. 49: 813-821.

15. Nord, S.G. and Young, R.F. (1975). Projection of tooth pulp afferents to the cat trigeminal nucleus caudalis. Brain Res. 90: 195-204.

16. Emmers, R. (1976). Thalamic mechanisms that process a temporal pulse code for pain. Brain Res. 103: 425-441.

17. Bloedel, J.R. (1974). The substrate for integration in the central pain pathways. Clin. Neurosurg. 21: 194-228.

18. Berkley, K.J. and Parmer, R. (1974). Somatosensory cortical involvement in responses to noxious stimulation in the cat. Exp. Brain Res. 20: 363-374.

19. Wall, P.D. and Sweet, W.H. (1967). Temporary abolition of pain in man. Science. 155: 108-109.

20. Higgins, J.D., Tursky, B. and Schwartz, G.E. (1971). Shock-elicited pain and its reduction by concurrent tactile stimulation. Science. 172: 866-867.

21. Campbell, J.N. and Taub, A. (1973). Local analgesia from percutaneous electrical stimulation. A peripheral mechanism. Arch. Neurol. 28: 347-350.

22. Larson, S.J., Sances, A., Riegel, D.H., Meyer, G.A., Dallmann, D.E., Swiontek, T. (1974). Neurophysiological effects of dorsal column stimulation in man and monkey. J. Neurosurg. 41: 217-223.

23. Friedman, H., Nashold, B.S., Jr. and Somjen, G. (1974). Physiological effects of dorsal column stimulation. In: J.J. Bonica, Editor. Advances in Neurology, Vol. 4. Pain. Raven Press. New York. pp. 769-773.

24. Shealy, C.N. (1974). Six years' experience with electrical stimulation for control of pain. In: J.J. Bonica, Editor. Advances in Neurology, Vol. 4. Pain. Raven Press. New York. pp. 775-782.

25. Long, D.M. and Hagfors, N. (1975). Electrical stimulation in the nervous system: the current status of electrical stimulation of the nervous system for relief of pain. Pain. 1: 109-123.

26. Meyer, G.A. and Fields, H.L. (1972). Causalgia treated by selective large fibre stimulation of peripheral nerve. Brain. 95: 163-168.

27. Shealy, C.N. (1974). Trancutaneous electrical stimulation for control of pain. In: R.H. Wilkins, Editor. Clinical Neurosurgery, Vol. 21. Proceedings of the Congress of Neurological Surgeons, Honolulu, Hawaii, 1973. Williams and Wilkins Company. pp. 269-277.

28. Burton, C. and Maurer, D.D. (1974). Pain suppression by transcutaneous electronic stimulation. IEEE Trans. Biomed. Eng. 21: 81-88.

29. Long, D.M. (1973). Cutaneous afferent stimulation for the relief of chronic pain. In: R.H. Wilkins, Editor. Clinical Neurosurgery, Vol. 21. Proceedings of the Congress of Neurological Surgeons, Honolulu, Hawaii, 1973. Williams and Wilkins Company. pp. 257-268.

30. Nathan, P.W. and Wall, P.D. (1974). Treatment of post-herpetic neuralgia by prolonged electric stimulation. Brit. Med. J, 3: 645-647.

31. Loeser, J.D., Black, R.G. and Christman, A. (1975). Relief of pain by transcutaneous stimulation. J. Neurosurg. 42: 308-314.

32. VanderArk, G.D. and McGrath, K.A. (1975). Transcutaneous electrical stimulation in treatment of postoperative pain. Amer. J. Surg. 130: 338-340.

33. Melzack, R. (1975). Prolonged relief of pain by brief, intense transcutaneous somatic stimulation. Pain. 1: 357-373.

34. Savara, B.S., Fields, R.W. and Tacke, R.B. (1975). Application of Electrical Current in Dental Anesthesia. Annual Summary Report, Contract No. DADA-17-70-C-0075, Dental Research Branch, U.S. Army Medical Research and Development Command, Washington, D.C. 20315. Dated November 14, 1975.

35. Fields, R.W., Savara, B.S. and Tacke, R. (1972). Regional electroanalgesia and its potentialities in control of orofacial pain. Oral Surg. 34: 694-703.

36. Savara, B.S., Fields, R.W. and Tacke, R.B. (1975). Application of Electrical Current in Dental Anesthesia. Annual Summary Report, Contract No. DADA-17-70-C-0075, Dental Research Branch, U.S. Army Medical Research and Development Command, Washington, D.C. 20315. Dated February 12, 1975.

37. Swets, J.A. (1973). The relative operating characteristic in psychology. Science 182: 990-1000.

38. Clark, W.C. (1974). Pain sensitivity and the report of pain: an introduction to sensory decision theory. Anesthesiology 40: 272-287.

39. Beecher, H.K. (1956). Limiting factors in experimental pain. J. Chron. Dis. 4: 11-21.

40. Michaelson, R.E., Seidberg, B.H. and Guttuso, J. (1975). An in vivo evaluation of inerface media used with the electric pulp tester. JADA 91: 118-121.

41. Greatbatch, W. Piersma, B., Shannon, F.D. and Calhoon, S.W., Jr. (1969). Polarization phenomena relating to physiological electrodes. Ann. N. Y. Acad. Sci. 167: 722-744.

42. Fields, R.W., Savara, B.S. and Tacke, R.B. (1977). Acupuncture in the Management of Injury and Operative Pain Under Field Conditions. Final Report, Contract No. DAMD-17-74-C-4090, U.S. Army Medical Research and Development Command, Washington, D.C. 20314. Dated February 2, 1977.

43. Greenwood, F. (1973). An electrophysiological study of the central connections of primary afferent nerve fibers from the dental pulp in the cat. Archs. Oral Biol. 18: 771-785.

44. Brookhart, J.M., Livingston, W.K. and Haugen, F.P. (1953). Functional characteristics of afferent fibers from tooth pulp of cat. J. Neurophysiol. 16: 634-642.

45. Mahan, P.E. and Anderson, K.V. (1970). Activation of pain pathways in animals. Amer. J. Anat. 128: 235-238.

46. Darian-Smith, I. (1966). Neural mechanisms of facial sensation. International Review of Neurobiology 9: 301-395.

47. Young, R.F. and King, R.B. (1972). Excitability changes in trigeminal primary afferent fibers in response to noxious and non-noxious stimuli. J. Neurophysiol. 35: 87-95.

48. Nord, S.G. and Ross, G.S. (1973). Responses of trigeminal units in the monkey bulbar lateral reticular formation to noxious and non-noxious stimulation of the face: Experimental and theoretical considerations. Brain Res. 58: 385-399.

49. Kaelber, W.W., Mitchell, C.L., Yarmut, A.J., Afifi, A.K. and Lorens, S.A. (1975). Center medianum - parafascicularis lesions and reactivity to noxious and non-noxious stimuli. Exp. Neurol. 46: 282-290.

50. Keller, O., Jastreboff, P. and Vyklicky, L. (1975). Anodal blocking of Aδ tooth pulp afferents. Brain Res. 87: 73-76.

51. Shigenaga, Y. and Inoki, R. (1976). Effect of morphine on single unit responses in ventrobasal complex (VB) and posterior nuclear group (PO) following tooth pulp stimulation. Brain Res. 103: 152-156.

52. Shigenaga, Y., Sakai, A. and Okada, K. (1976). Effects of tooth pulp stimulation in trigeminal nucleus caudalis and adjacent reticular formation in rat. Brain Res. 103: 400-406.

53. Yokota, T. (1976). Two types of tooth pulp units in the bulbar lateral reticular formation. Brain Res. 104: 325-329.

54. Savara, B.S., Fields, R.W., Tacke, R.B. and Tsui, R.S.H. (1974). Modulation of cortical inputs from tooth pulp by electrical stimulation of adjacent gingiva. Oral Surg. 37: 17-25.

55. Fields, R.W., Tacke, R.B. and Savara, B.S. (1975). The origin of trigeminal response components elicited by electrical stimulation of the tooth pulp of the cat. Archs. Oral Biol. 20: 437-443.

56. Fields, R.W., Tacke, R.B. and Savara, B.S. (1975). Pulpal anodal blockade of trigeminal field potentials elicited by tooth stimulation in the cat. Exp. Neurol. 47: 229-239.

57. Fields, R.W., Beale, R.J., Tacke, R.B. and Savara, B.S. (1975). Unit activity in the Gasserian ganglion elicited by cat tooth pulp stimulation. Neurosci. Abst. 1: 152.

58. Fields, R.W., Tacke, R.B., Beale, R.J. and Savara, B.S. (1976). Prolonged post-block hypoexcitability induced by anodal blockade of cat tooth pulp. Exp. Neurol. 50: 293-303.

59. Fields, R.W., Tacke, R.B., O'Donnell, R.P. and Savara, B.S. (1976). Afferent excitability compared using pulsating versus constant direct current electroanalgesia in cat tooth pulp. Exp. Neurol. 53: 386-398.

60. Fields, R.W., Tacke, R.B., O'Donnell, R.P. and Savara, B.S. (1976). Effects of simulated acupuncture stimulation on pulp-driven thalamic unit activity. Neurosci. Abst. 2: 934.

61. Ross, G.S. (1966). A technique to study pain in monkeys: Effects of drugs and anatomic lesions. In: R.S. Knighton and P.R. Dumke, Editors. Pain. Little, Brown and Company. Boston, Mass. pp. 91-110.

62. Bitterman, M.E. (1966). Animal learning. In: J.R. Sidowski, Editor. Experimental Methods and Instrumentation in Psychology. McGraw-Hill. New York. Chap. 11.

63. Reid, K.H. (1972). Reflex and behavioral withdrawal responses to tooth pulp stimulation. Soc. for Neurosci. Abstr. 1972.

64. Belluzzi, J.D. and Grossman, S.P. (1973). A source of scrambled constant current with solid state control. Physiol. Behav. 10: 133-135.

65. Kelly, D.D. and Glusman, M. (1971). Behavioral contrast: An unlocalized effect of a localized anesthetic. Physiol. and Behav. 7: 837-840.

66. Coffer, C.M. and Appley, M.H. (1964). Motivation. John Wiley. New York.

67. Sidowski, J.B. (1966). Experimental Methods and Instrumentation in Psychology. McGraw-Hill, Inc. New York.

68. Mumford, J.M. (1973). Toothache and Related Pain. Churchill Livingstone. Edinburgh and London.

69. Newman, P.P. (1973). Electrical method for controlling pain. Nature. 243: 474-475.

70. Winer, B.J. (1971). Statistical Principles in Experimental Design. 2nd Ed., McGraw-Hill. New York. 1971. pp. 198-261.

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